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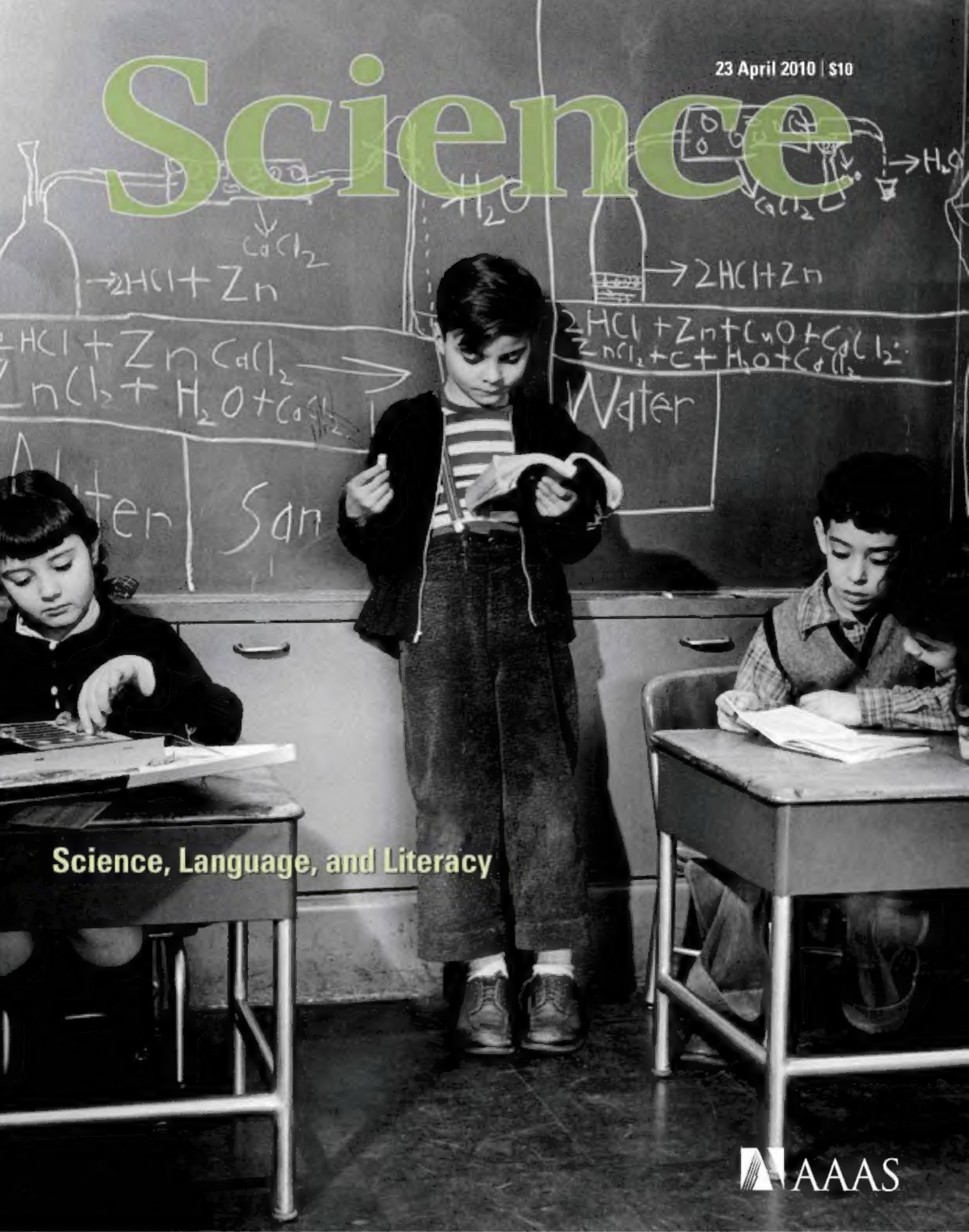
Science



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SPECIAL SECTION

Science, Language, and Literacy

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COVER

Children learning science, like these 7-year-olds tackling nuclear physics in 1948, must work through their mistakes and misconceptions. The route to science literacy involves reading, debate, presentation, and writing. See the special section beginning on page 447.

Photo: Nina Leen/Time Life Pictures/Getty Images

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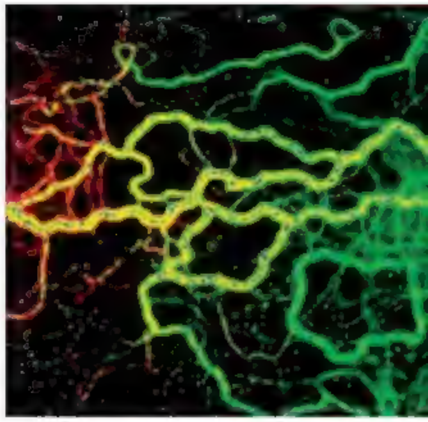
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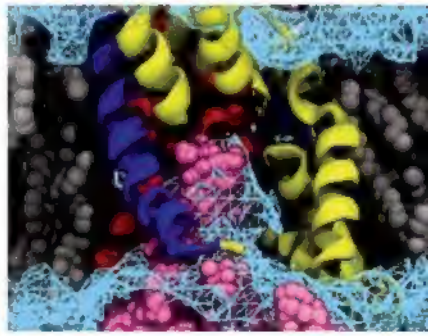
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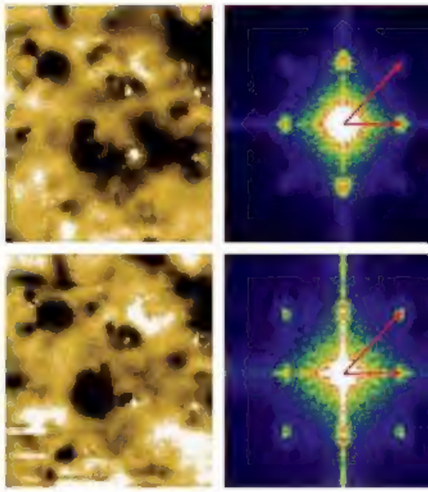
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D. Pires et al.
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10.1126/science.1187851

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A. Molnar et al.
10.1126/science.1187959

Small RNA Duplexes Function as Mobile Silencing Signals Between Plant Cells
P. Dunoyer et al.
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10.1126/science.1185880

Neural Crest–Derived Pericytes Promote Egress of Mature Thymocytes at the Corticomedullary Junction
M. A. Zachariah and J. G. Cyster
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T. Gregor et al.
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S. Webb
A complex fabric of researchers work to understand and treat autism.

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E. Pain
Faculty who teach science to nonmajors promote science literacy overall.
>> Science, Language, and Literacy section p. 447 and www.sciencemag.org/special/education2010/

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A. Potti et al.
Success in cancer therapy requires new strategies for matching treatments with individual patients.

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Understanding the puzzle of autism

PERSPECTIVE: Drug Resistance, Epigenetics, and Tumor Cell Heterogeneity
T. Hoey
Acquisition of drug resistance can occur through changes at the chromatin level in subpopulations of cancer cells.

RESEARCH ARTICLE: Lentiviral Overexpression of GRK6 Alleviates L-DOPA–Induced Dyskinesia in Experimental Parkinson's Disease
M. R. Ahmed et al.
G protein–coupled receptor kinase 6 alleviates dyskinesia without compromising the antiparkinsonian effect of L-DOPA.

RESEARCH ARTICLE: Brief Suppression of *Abcc8* Prevents Autodestruction of Spinal Cord After Trauma
J. M. Simard et al.
Secondary injury that occurs after trauma to the spinal cord can be prevented by inhibiting expression of the gene for a calcium transporter.

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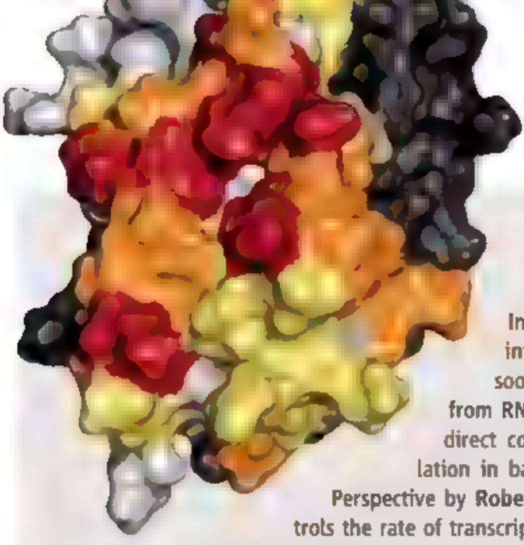
EDITED BY CAROLINE ASH



<< Transcription and Translation in Train

In bacteria, translation of messenger RNA into proteins by the ribosome usually begins soon after the ribosome binding site emerges from RNA polymerase. Now there is evidence for direct coupling between transcription and translation in bacteria. **Proshkin et al.** (p. 504; see the Perspective by **Roberts**) show that the trailing ribosome controls the rate of transcription by preventing RNA polymerase from spontaneous backtracking, which allows precise adjustment of transcriptional yield to translational needs under various growth conditions. **Burmann et al.** (p. 501; see the Perspective by **Roberts**) provide a potential mechanism for coupling by showing that the transcription factor NusG, which binds RNA polymerase through its amino-terminal domain, competitively binds either a ribosomal protein or the Rho transcription termination factor through its carboxy-terminal domain. Rho binding might occur after release of the ribosome from messenger RNA, thus linking termination of transcription and translation.

Triangulating to Mechanism

Cellular uptake and release of a variety of substrates are mediated by secondary transporters, but no crystal structures are known for all three fundamental states of the transport cycle, which has limited explanations for their proposed mechanisms. **Shimamura *et al.*** (p. 470) report a 3.8-angstrom structure of the inward-facing conformation of the bacterial sodium benzylhydantoin transport protein, Mhp1, complementing the other two available structures. Molecular modeling for the interconversions of these structures shows a simple rigid body rotation of four helices relative to the rest of the structure in which the protein switches reversibly from outward- to inward-facing.

Breaking Convention

The defining characteristics of a superconductor are symmetry of gap function, which tells us something about how pairs of electrons move through the sample, and the strength of that pairing. Together, this information gives us the highest temperature to which the superconductor can remain superconducting. In conventional superconductors the gap function is symmetric, or s-wave, and tends to have low transition temperatures. The newly discovered iron-based superconductors also have *s*-wave symmetry, but the rather high transition temperatures, in addition to other properties, indicate that they are not conventional. **Hanaguri *et al.*** (p. 474; see the Perspective by **Hoffman**) use scanning tunneling microscopy to provide direct experimental confirmation of the unconventional *s*-wave pairing of the superconducting carriers in these materials.

CREDITS (TOP TO BOTTOM): BURMANN ET AL.; MATZEL ET AL.

Microcapacitors for Manufacture

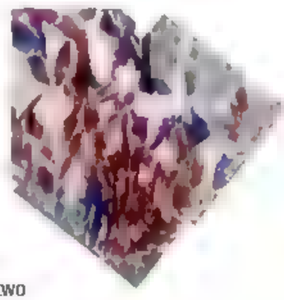
Capacitors can store small amounts of charge, and as they can charge and discharge quickly, they work well with batteries for recovering power, such as in regenerative braking in hybrid cars. For very small power requirements, capacitors have not been competitive with microbatteries, but using monolithic carbon films to store the charge, **Chmiola *et al.*** (p. 480) demonstrate the feasibility of such applications. The small pores in the carbon films are sufficiently large to allow electrolyte transport and can be made using a processing technique compatible with current chip manufacturing. Such microcapacitors can thus be integrated with electronics to make autonomous sensors or implantable devices.

Nanosynthesis Without a Twist

The synthesis of many nanoscale materials occurs under conditions of changing saturation because generation of product decreases the concentration of reactants. **Morin *et al.*** (p. 476) used a flow reactor to maintain conditions of low supersaturation during the growth of zinc oxide nanotubes and nanowires. Under these conditions, growth of the tubes was controlled by the release of stress, which prevented the torquing of the crystals along their axis. Since growth at different saturation conditions matched predictions, this looks like a promising method to develop rational and controlled synthesis of nanomaterials at large scale and low cost.

Sun Stuff

Comets are thought to be remnants of the Sun's protoplanetary disk; hence, they hold important clues to the processes that originated the solar system. **Matzel *et al.*** (p. 483, published online 25 February) present Al-Mg isotope data on a refractory particle recovered from comet Wild 2 by the NASA Stardust mission. The lack of evidence for the extinct radiogenic isotope ^{26}Al implies that this particle crystallized 1.7 million years after the formation of the oldest solar system solids. This observation, in turn, requires that material formed near the Sun was transported to the outer reaches of the solar system and incorporated into comets over a period of at least two million years.



Of Monsoons and Megadroughts

The Asian monsoon is the weather system that has the greatest effect on the greatest number of people in the world. Naturally then, knowing better how climate change might affect the monsoon is tremendously important. One obstacle that prevents a better understanding of future behavior is a poor knowledge of its past. **Cook *et al.*** (p. 486; see the Perspective by **Wahl and Morrill**) help to fill this gap with a 700-year reconstruction of the monsoon from tree-ring data obtained throughout Asia. The reconstruction chronicles monsoon failures and megadroughts, as well as patterns of precipitation, and can thus be compared with other relevant climate records to allow links with sea-surface temperatures to be better understood.

Separated About Lift

The uplift history of the Andes of South America is a contentious issue, with the two main hypotheses polarizing from rapid growth between

Continued on page 404

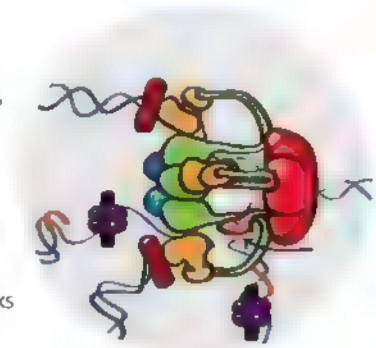
Continued from page 403

roughly 10 and 7 million years ago to more gradual elevation over most of the past 40 million years. The oxygen isotopic composition of soil carbonates has been used as a proxy for altitude and to measure the timing of uplift. **Poulsen *et al.*** (p. 490, published online 1 April) applied a global atmospheric general circulation model to show that the oxygen isotopic composition changes seen in carbonates formed in the late Miocene were driven more by changes in the amount of precipitation than by the altitude at which the precipitation forms. Consequently, it seems that oxygen isotopes are not a reliable paleoaltimeter, and Andean uplift may not have been as precipitate as thought.

A Little Selection for a Lot of Rarity

Studies on how selection works have tended to focus on the effect of a single trait. This necessarily means that rare alleles that can be acted on by selection appear to experience high levels of frequency-dependence selection. However, selection may act on multiple traits at any one time. **Doebeli and Ispolatov** (p. 494) present a theoretical framework examining how multiple rare traits can persist and potentially drive speciation. The authors show that only low levels of frequency-dependent selection are needed to explain the observed high levels of allelic diversity in nature.

Forking Replisomes



Replisomes are multiprotein machines that replicate DNA. Significant insight into how they work comes from in vitro studies, but how replisomes are organized in living cells has remained unclear. **Reyes-Lamothe *et al.*** (p. 498) have watched the replisome in living *Escherichia coli* cells using single-molecule fluorescence spectroscopy with millisecond time resolution. Cells expressing fluorescent derivatives of 10 different replisome components revealed both the stoichiometry and spatial distribution of the components at active replication forks in *Escherichia coli*. A similar technique could be used to study other molecular machines as they function.

HIV and *Salmonella*

HIV-positive individuals who are infected with nontyphoidal strains of *Salmonella enterica* often succumb to high morbidity and mortality. Why this is the case is unknown. **MacLennan *et al.*** (p. 508; see the Perspective by **Moir and Fauci**) have uncovered a dysregulated antibody response to *Salmonella* that is the likely culprit. Sera from HIV- infected individuals do a poor job of killing *S.* Typhimurium, despite surprisingly elevated antibody titers. Experiments showed that HIV-infected serum inhibited the power of normal serum to kill *Salmonella*. Inhibition was specific to antibodies against lipopolysaccharide (LPS), a component of the cell wall of *Salmonella*. Hence, HIV-infected sera was able to kill *Salmonella* strains lacking LPS, and removing LPS immunoglobulin G from infected sera permitted *Salmonella* killing. Thus, not only does HIV cause defects in cell-mediated immunity but it also seems to impair humoral immunity, with severe consequences for multiple infections.

Reading Influences and Achievement

When it comes to learning to read, children are immersed in a variety of influences. Debate rages over what aspects are affected and what importance to attribute to genetic influences, the effect of good teaching, the tools used, the family environment, and so on. **Taylor et al.** (p. 512) analyzed reading achievement from kindergarten through to fifth grade in mono- and dizygotic twins from a diverse population. The results show that better teachers allow children to fulfill their genetic potential.

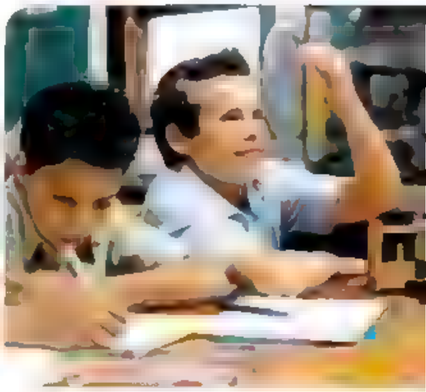
CREDIT: REYES-LAMOTHE ET AL

Prioritizing Science Education

Bruce Alberts is Editor-in-Chief of *Science*

IN THIS SPECIAL ISSUE ON EDUCATION, *SCIENCE* FOCUSES ON THE CONNECTION BETWEEN LEARNING science in school and the acquisition of language and communication skills, emphasizing the benefits of teaching science and literacy in the same classrooms whenever possible. In the United States, this would be viewed as a radical proposal. Unfortunately, the great majority of Americans are accustomed to science classrooms where students memorize facts about the natural world and, if they are lucky, perform an experiment or two; in language arts classes, students generally read fictional literature and write about it in fossilized formats such as "compare and contrast."

The exciting news, affirmed in many articles in this issue, is that "science learning entails and benefits from embedded literacy activities [and]…literacy learning entails and benefits from being embedded within science inquiry."* Here, it is helpful to distinguish between factual (or informational) and fictional (or narrative) text. Science reading and writing is largely of the former type, and it is this factual, informational text that dominates today's knowledge-everywhere world. Yet, most of the formal teaching in language arts classrooms deals with fictional text. My own failed efforts at storytelling lacked the imagination to do anything more than rewrite Hansel and Gretel in a thinly disguised new context. Without doubt, learning to write and read clear and concise informational text, as in summaries of investigations in science class, is an essential preparation for nearly all of life out of school.



By reconceptualizing science education through closely connecting literacy lessons with active inquiry learning in science class, one can make a strong argument for greatly expanding the time spent on science in primary school, to at least 4 hours a week. This alone would carry tremendous benefit in places where, like the United States, science for young students has often become marginalized to less than an hour a week.

A second advantage to forging this connection between literacy and science teaching is that a well-taught science class gives everyone a chance to excel in something. It is hard to stay motivated and interested in schooling if one is always in the bottom half of the class. By linking literacy and science education, those who are more challenged with making progress in reading can gain the self-confidence needed to succeed by demonstrating skills in analyzing a problem that stumps the better readers. Or they might excel in the mechanical manipulation of objects required in a science lesson. From this perspective, the penalties for "failing" schools in my home state of California are tragically wrong. Students who struggle with reading or math are given double periods of reading or math drill, and the very set of activities that could excite them about school is eliminated.

I am reminded of the schooling of P. Roy Vagelos, an outstanding scientific leader in U.S. academia and industry. A fellow biochemist and a friend, Roy topped off his career by becoming the chief executive officer of the major pharmaceutical company Merck, with *Fortune* magazine anointing his company as the "most admired in America" for seven successive years (1987 to 1993). In his biography, he describes himself as a poor memorizer, who nearly failed first and second grade and was largely alienated from school until he was given the chance to demonstrate other skills that allowed him to excel.†

How many talented young people are we losing in today's schools, driven by test scores that reward teachers for drilling students to remember obscure science words, and by an early reading curriculum based on stories and folk tales? Instead, we should be rewarding them for teaching science inquiry skills and literacy together, through collaborative and critical discourse.‡

–Bruce Alberts

10.1126/science.1190788

*P. D. Pearson, E. Moje, C. Greenleaf, *Science* **328**, 459 (2010). †P. R. Vagelos, L. Galambos, *Medicine, Science, and Merck* (Cambridge Univ. Press, Cambridge, 2004). ‡J. Osborne, *Science* **328**, 463 (2010).

EDITED BY GILBERT CHIN AND JAKE YESTON

EDUCATION

Contextual Teaching

Can integrated approaches to literacy instruction alleviate the disadvantages and poor performance of students in urban schools, and are there differential effects on students not native to the language of the school system? Lesaux *et al.* have developed a program to improve a foundational element of reading comprehension—vocabulary. The 18-week intervention involved sixth-grade teachers and 500 of their students, roughly three-quarters of whom were not native English speakers, from urban schools. The program differed from traditional instruction in several ways: (i) Rather than memorizing lists of words and definitions, students read passages from texts describing real-world events; (ii) rather than literature-based texts, students read expository, nonfiction text from a news magazine; (iii) academic words (such as evidence and method) that appear across a range of disciplines were emphasized; and (iv) students didn't just read, but also discussed and wrote passages. Multilevel modeling indicated that this regimen improved students' abilities to understand words in multiple forms (for instance, complex versus complexity) and in multiple contexts. Results on a measure of reading comprehension were promising, and this program was comparably effective for native and non-native English speakers. Two challenges must be met if such research is to contribute at scale: Interventions must be efficacious yet also easily implemented and maintained in mainstream classroom settings. Observation, surveys, and interviews revealed that program materials and training empowered teachers to implement the program with good fidelity. — BW

Reading Res. Quart. **45**, 196 (2010).

BIOTECHNOLOGY

Positive Reinforcement

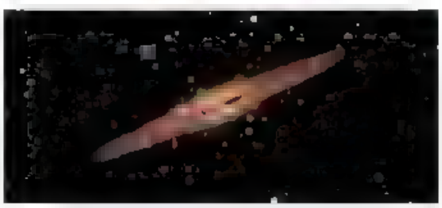
It's often easier, when formulating rules, to tell people what not to do. Positively encouraging desirable behavior requires all manner of subtle distinctions that simple prohibitions avert. A similar contrast arises in efforts to direct the behavior of bacteria. Advances in genetic engineering have recently enabled researchers to modulate the internal chemistry of organisms such as *Escherichia coli* in order to favor excess production of a particular metabolite of commercial interest—a strategy prized for its chemical efficiency and waste minimization relative to synthetic elaboration of petroleum feedstocks. The modulation is straightforward when it entails deleting genes that disrupt the path to the desired product; determining which genes may need a boost is rather more complicated, given the interconnected nature of the cell's network of metabolic reactions. Choi *et al.* have developed a method of simulating metabolic flux for the express purpose of predicting which genes ought to be amplified in order to optimize production of a particular target compound. They demonstrate the method by optimizing for lycopene production in *E. coli*. Though not every gene identified in the simulation proved beneficial to amplify in practice, the method showed significant promise, particularly in tandem with a more traditional gene knockout simulation. — JSY

Appl. Environ. Microbiol. **76**, 10.1128/AEM.00115-10 (2010).

ASTRONOMY

Whence the Spirals?

Observations of the Milky Way and its nearest spiral neighbor, Andromeda, suggest that the outer stellar regions of these galaxies assembled by accretion of smaller, satellite galaxies. How common is this process in shaping such large spiral galaxies? Using the Subaru



Telescope in Hawaii, Mouhcine *et al.* surveyed the outer regions of NGC 891, a spiral galaxy analogous to the Milky Way but located 30 million light-years away and thus well outside our immediate vicinity. The map of stars around this galaxy shows signs of tidal interactions and satellite disruption, including arc-like streams, one of which loops all the way around the galaxy. Together with observational evidence from other galaxies, this result suggests that accretion of small satellites may indeed be a common process in the formation of spiral galaxies. NGC 891 is also surrounded by a thick envelope of stars, which may have resulted from tidal disruption of several small satellite galaxies. This may also be a common property of large spiral galaxies. — MJC

Astrophys. J. **714**, L12 (2010).

PLANT SCIENCE

Cell Wall Construction

Lignin, a heterogeneous polymer built from *p*-hydroxycinnamyl monomers, provides the stiffness in woody tissues of vascular plants. The resiliency of lignin may be useful to a tall tree,

but it is an obstacle in the extraction of sugars from plant tissues that are used as biofuels. Angiosperms use a larger set of subunits—featuring monomers in which hydroxylation at both *meta* positions has occurred—to make lignin than do most plants in the lycophyte lineage, which diverged from the angiosperm lineage 400 million years ago. Weng *et al.* have identified a cytochrome P450 enzyme from the lycophyte *Selaginella* that bears limited similarity to angiosperm enzymes, and when the *Selaginella* enzyme was introduced

into the angiosperm *Arabidopsis*, a new form of lignin was detected. These results suggest that the enzymatic diversity of the broader plant kingdom might be informative for taming recalcitrant biosynthetic pathways in potential biofuel crops. — PJH

Plant Cell **22**, 10.1105/tpc.109.073528 (2010).

EVOLUTION

Three Little Unexpected Children

The genetic code consists of triplets of nucleotides (codons) that are read by complementary triplets (anticodons) in amino acid–carrying tRNAs; for example, the codon CAU is read by an AUG-anticodon in tRNA charged with the amino acid histidine (His). Charting the evolution of the triplets is complicated because almost nothing is known of what came before. The stereochemical hypothesis suggests that codons or anticodons arose through specific recognition of their cognate animo acid. Johnson and Wang looked through the three-dimensional structures of ribosomes from four different species to see if any of the amino acids in the ribosomal proteins might be found in the vicinity of their respective codon or anticodons in the ribosomal RNAs. Although no amino acids were preferentially enriched near their contemporary codons, 11 amino acids were found close to their anticodons. It has been proposed that these 11 amino acids joined the primordial genetic code later on, perhaps during the concurrent evolution of a primitive translation system. Statistical analysis of 4 of the 11 amino acids suggests that they underwent reassignment; His was initially coded by four codons—CAU, CAC, CAA, and CAG—but CAA and CAG were subsequently ceded to the upstart glutamine. — GR

Proc. Natl. Acad. Sci. U.S.A. **107**, 10.1073/pnas.1000704107 (2010).

CREDIT: JING-KE WENG

EDUCATION

All Three R's in Science

Writing and argumentation skills are critical to the successful scientist, yet they are often overlooked in science curricula. Do such abilities transfer well from classes in more literacy-focused disciplines? Part of a recent study by Adams *et al.* investigates whether undergraduate students revising scientific texts are able to recognize and address discrepancies in structure and argument or whether they focus mainly on spelling and grammar. The study assessed vocabulary, content knowledge, and verbal memory of 48 students in the first year of a psychology degree program. Students were asked to analyze scientific texts containing errors in three categories: language, structure (i.e., lack of conclusion), and argument (i.e., lack of evidence). The results showed that students were better able to identify errors of language and structure than of argument, and topic knowledge and verbal working memory seemed to be less important than verbal short-term memory. Although this study highlights the importance of teaching literacy skills specifically attuned to science classes, further research is needed to assess whether a lack of genre knowledge accounts for the lack of identification of argument errors. — MM

J. Res. Reading **33**, 54 (2010).

DEVELOPMENT

Moving In and Settling Down

In stem cell–based therapeutic strategies aimed at restoring the function of neural tissue, the proliferation, differentiation, and migration of introduced neural precursor cells must be tightly controlled. Delaloy *et al.* have examined microRNA (miRNA) expression as human embryonic stem cells differentiated into postmitotic neurons in cell culture and found that miRNA-9 (miR-9) increased in human neural progenitor cells (hNPCs) before terminal differentiation. In a mouse model of stroke, miR-9 loss of function resulted in a decrease of cell proliferation and an increase in migration of hNPCs that had been transplanted into ischemic mouse brain. Hence, miR-9 appears to coordinate early hNPC proliferation and delay early hNPC migration, properties that will be of use in designing potential treatments for brain or spinal cord injury. — BAP

Cell Stem Cell **6**, 323 (2010).

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AAAS
ADVANCING SCIENCE, SERVING SOCIETY

EDITED BY LAUREN SCHENKMAN

Playful Shapes

Wildly distorting mirrors and twisting tunnels of stacked shapes are among the math-inspired attractions for children and adults at the Geometry Playground, a group of 20 exhibits opening 25 June at the Exploratorium in San Francisco, California. Exhibit director Thomas Rockwell says the toys and structures combine "hands-on with body-in geometry" to "create a playground for the body and mind." Until opening day, Rockwell says, he and Exploratorium science education researcher Joshua Gutwill are using the playground as a lab for studying how "navigation or climbing through structures involves spatial reasoning."

Precious Metal

In about 50 B.C.E., a Roman ship set sail from Spain and headed toward Italy carrying hundreds of lead bricks. More than 2000 years later, the approximately 30-meter-long vessel's cargo—a vital commodity that was used in everything from water ducts to sling bullets—is being incorporated into an experiment designed to investigate the fundamental constituents of nature.

The ship sank off the coast of Sardinia and remained on the sea floor until an amateur scuba diver discovered it 20 years ago. By then, atoms of the radioactive isotope originally in the lead had decayed, leaving it almost entirely radioactively inert—and thus ideal for shielding ultrasensitive nuclear physics experiments from external sources of radiation.

So when the Italian National Institute of Nuclear Physics (INFN) heard of the hoard, it eagerly helped fund the excavation by the National Archaeological Museum in Cagliari in exchange for 150 of the 33-kilogram bricks. Last week, another 120 of the Roman ingots arrived at INFN's Gran Sasso high-energy physics laboratory in central Italy. They will be cleaned and melted down to line the CUORE experiment, which watches for an extremely rare nuclear event—neutrinoless double beta decay—in hopes of learning the mass of the neutrino and whether it is its own antiparticle. "For us, this lead really is treasure," says Ettore Fiorini, nuclear physicist and CUORE spokesperson.

Ötzi Redux

Ötziphiles have a great year to look forward to in 2011. That's when the museum of archaeology in Bolzano, Italy, will be celebrating the 20th anniversary of the discovery of the 3500-year-old Iceman in an Alpine glacier.

The exhibition, to open in March, will feature a brand-new reconstruction of the Iceman by the brothers Adrie and Alfons Kennis of Arnhem in the Netherlands. Alfons says many reconstructions of ancient humans look too pale and "fresh from the shower." The Kennises, who will base the reconstruction on 3D scans of the head and body, envisage a brown-skinned, weather-beaten figure with some bruises and scratches, trudging through the snow. It being spring, he had probably shed some of his clothes, Alfons says, but his face probably had telltale black pits from frostbite. "We want to show a little bit of his body," including tattoos on legs and back, adds Alfons. As it would be "too dramatic" to show an arrow in his back, they'll probably portray Ötzi as he might have been just before being hit by what probably killed him. "His facial expression will be tricky," says Alfons; he should look worried but "not too frantic." Ötzi's mouth will be partly open to show the big gap in his front teeth. "People who knew him probably knew him best from his teeth," says Alfons.

Old-model Iceman now in the Bolzano museum.

The world's killer whales (*Orcinus orca*) have long been regarded as a single species. But researchers say their new analysis of orca DNA suggests that three populations are genetically different enough to be individual species.

Scientists suspected as much because killer whale populations vary greatly in diet (some are strict fish-eaters; others dine on only marine mammals), size, markings, and behavior. But previous analyses "showed very little genetic diversity" in orcas, says the current study's lead author, geneticist Phillip Morin of the National Oceanic and Atmospheric Administration's Southwest Fisheries Science Center in San Diego, California. Whereas those earlier analyses looked at only small portions of the whales' mitochondrial DNA, Morin's team surveyed the entire mitochondrial genome, in 139 samples of orcas from the North Pacific, North Atlantic, and Southern Hemisphere oceans. Now up for species-hood: a dwarf form of fish-eating orca in the Ross Sea; a larger "pack-ice" orca that hunts seals in the Antarctic; and a marine mammal–hunting orca of a population known as North Pacific Transients.

The new study, which appears this week in *Genome Research*, "is exciting and will certainly help settle the debate" about variation in killer whales, says Robin Baird, a cetacean expert with Cascadia Research Collective in Olympia. Researchers also hope that it will lead to better conservation practices targeted at the needs of each species.

CREDITS (TOP TO BOTTOM): EXPLORATORIUM; INSTITUTO NAZIONALE DI FISICA NUCLEARE; SOUTH TYROL MUSEUM OF ARCHAEOLOGY/A. KAISER; DAVE ELL FRIT NOAA ALASKA FISHERIES SCIENCE CENTER

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VOLCANOLOGY

Iceland Eruptions Fuel Interest in Volcanic Gas Monitoring

REYKJAVIK—As a brown cloud of ash drifts down from the slopes of Eyjafjallajökull toward their truck, Hanna Kaasalainen warns a colleague that their gas masks won't be much good against carbon dioxide. The masks filter out poisonous gases released by magma such as sulfur dioxide, but carbon dioxide can simply displace oxygen in the air, asphyxiating the researchers as they take ash samples alongside a haze-enshrouded, deserted road. "We shouldn't stay very long," the University of Iceland geochemistry graduate student advises, before strapping on a bright yellow mask and opening the door.

The samples Kaasalainen promptly begins collecting are just one of several streams of data that Icelandic researchers and civil protection officials are continually analyzing to make educated guesses about the duration and size of the eruption on Eyjafjallajökull, the volcano that on Wednesday, 14 April, turned from a modest tourist attraction into a nightmare for airlines and passengers across Europe. Everyone wants to know if the volcano's ash cloud, harmful to jet engines, is going away or will remain a threat. At a briefing here called on 19 April to share the latest observations, University of Iceland geophysicist Páll Einarsson summed up the frustrating conclusion: Despite all the data, "we are still looking for an answer."

Thanks to Eyjafjallajökull, scores of volcanologists, geologists, and other scientists are now focusing their attention on the southern coast of Iceland. Some are analyzing GPS measurements, seismic readings, and satellite images. Others, like geochemist Michael Burton of the Istituto Nazionale di Geofisica e Vulcanologia in Catania, Italy, are measuring gas emissions that give hints about volcanic behavior. Burton, part of a team monitoring the Mount Etna and Stromboli volcanoes in Italy, flew here shortly after Eyjafjallajökull's initial eruption on the night of 20 March. His hope is that combining information on gas emissions with traditional volcanology data will better explain the behavior of volcanoes before and during eruptions.

In the early days of its latest eruption, however, Eyjafjallajökull remained unpredictable. And some scientists wonder whether the volcano's recent bursts are a practice run for potentially more disruptive eruptions in Iceland. The last blasts from Eyjafjallajökull, in 1612 and 1821, each preceded larger eruptions from Katla, to the east. And the tragic story of Laki, the volcano just under 100 kilometers from Eyjafjallajökull, looms in the back of Icelanders' minds. Its eruptions from 1783 to 1785 released a cloud of hydrogen fluoride that coated fields and infiltrated groundwater in Iceland and generated an ash cloud that cast its shadow across Europe. According to some researchers, the resulting poisoning of livestock in Iceland and the cooling effect of the ash may have hurt Europe's agricultural productivity enough to cause thousands of deaths; the fluoride may have even directly poisoned people (*Science*, 19 November 2004, p. 1278).

Eyjafjallajökull's so-far-unpredictable behavior offers a perfect example of the challenge facing volcanologists. Before this spring's first eruption, geophysicists at the University of Iceland and their counterparts at the Icelandic Meteorological Office (IMO) noticed GPS stations on the volcano had wandered several centimeters in May of 2009 and again in December, signs that rising magma was stretching the skin of the volcano in advance of an eruption. In mid-February, Sigrún Hreinsdóttir, a geophysicist at the University of Iceland, placed an additional GPS station on the mountainside. By then, Steinunn Jakobsdóttir, a geophysicist at IMO, was tracking automatic seismic reports that revealed tremors about 5 kilometers below Eyjafjallajökull's surface. In March, civil authorities alerted nearby residents that they were at risk of floods called *jökullhlaups*, literally "running glaciers," if the ice-covered volcano erupted.

But officials didn't order evacuations because the seismic hints weren't that dire. "Usually when an eruption starts, a low-frequency [seismic signal] is rising when the magma is coming to the surface," says Jakobsdóttir. Although seismic tracking placed magma closer to the surface on 19 March, this low-frequency signal was absent, so civil authorities kept the alert level at its lowest setting. But the next night, southern Icelanders reported a dark cloud glowing red above the mountain: The volcano had experienced a small eruption, one that led authorities to evacuate farmers living in its floodplains. "We missed [any] short-term warning," says Jakobsdóttir ruefully.

That's why Burton and Icelandic researchers plan to pay closer attention to the smells of the volcanoes here. A few days after they arrived last month, Burton and colleagues drove a candy-red Land Cruiser with over-

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A national environment observatory
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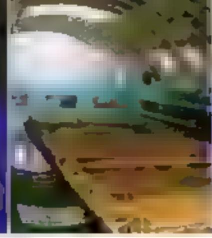

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sized tires onto the black gravel where the March eruption took place. On that mountain pass, they measured sulfur dioxide using a UV-sensitive digital camera and spectroscopes. Combined with seismic readings and knowledge of the magma's composition prior to the eruption, such gas emission data can help researchers estimate the volume of magma rising beneath the surface. "Seismic tremors tell you where things are happening, and it tells you in a way the intensity with which things are happening," notes Burton, "but it doesn't tell you volume; … that's what makes these two systems extremely complementary."

Analyzing gas emissions from dormant and active volcanoes is a growing trend. "Not all eruptions start with a bang," notes IMO geophysicist Kristín Vogfjörd, who is pushing to add volcanic gas detectors to Iceland's seismic, GPS, and strain monitoring systems. Indeed, the promise of integrating gas emission studies with other volcano monitoring systems has attracted European funding for a pair of networks that have monitored nearly two dozen volcanoes from Central America to Iceland over the last 5 years. As a result, researchers armed with increasingly portable and affordable instruments are deciphering the gas signatures of distinct kinds of magma, much as a beer brewer might recognize stages of fermentation and different beers with a mere wrinkle of the nose.

Magma-released volcanic gases proved their predictive power in 1998. Although seismic signals from magma had tapered off, volcanologists heeded gas signals that Montserrat was not done erupting and thus avoided a potential disaster when the volcano began erupting again in 1999 (*Science*, 28 March 2003, p. 2027).

Since then, interest in gas geochemistry has steadily risen among volcanologists, according to Michael Poland of the U.S. Geological Survey's Hawaiian Volcano Observatory (HVO) in Hawaii National Park, who himself stuck to monitoring land deformation until he had an eruptive epiphany. In early 2008, HVO staff met to discuss unusually high amounts of sulfur dioxide venting from the Hawaiian volcano Kilauea. Poland thought a summit eruption "was out of the question, since there was no deformation or seismicity indicating magma ascent," but a gas geochemist argued that one was imminent. Poland laid a wager. If the volcano erupted, the geophysicist would become a gas geochemist or quit his job.

Kilauea erupted explosively three times within a month.

Poland has been true to his word. He now says that incorporating gas geochemistry is "absolutely essential for really good monitoring of volcano activity." Last year, in the 27 August 2009 issue of *Geophysical Research Letters*, he and USGS colleague A. Jeff Sutton, a gas geochemist, reported that another instance of Kilauea volcanic activity preceded by sulfurous fumes in 2007 could be explained if the magma that left the summit chamber for a side vent lowered local pressure enough to release gases, including sulfur dioxide, that had been in solution in the magma.

Fire and ice. Iceland's southern coast is home to volcanoes big and small.

Burton and his Italian collaborators have also had success relating volcanic gas activity to eruptive activity. "Only about 10% of magma which is degassing ever comes out," he says, so researchers need to establish detailed relationships between physical signals such as deformation and degassing to predict accurately when magma will emerge (*Science*, 3 August 2001, p. 774). Burton uses a webcam in his Pisa, Italy, office to guide the latest gas spectroscopy instruments on Stromboli. The team has also used portable infrared spectroscopes there to analyze gases exploding from the volcano's crater and to compare them with gases emerging when the volcano is quiet. The ratio of chemicals in the gases helped the team estimate the temperatures through which the exploding gases passed and depth at which they separated from the magma—a new kind of measurement (*Science*, 13 July 2007, p. 227).

Setting up a gas monitoring network good enough to predict anything isn't easy. The UV spectroscopes, for example, rely on a clear line of sight—they need a light source, such as the sun, behind a gas plume. Iceland is particularly tricky for gas detection. Glaciers cover volcanic vents, and frost, wind, and rain would bedevil stationary gas monitoring equipment. "We don't really know … where to put these gas monitors," says Magnús Tumi Guðmundsson of the University of Iceland.

Getting close enough to a vent to detect gases can also be lethal, as a 1993 accident that killed six scientists on the Galeras volcano in Colombia demonstrated (*Science*, 16 April 1993, p. 289). Such difficulties are why seismometers, not gas monitors, remain the frontline tool on most closely monitored volcanoes. "Seismicity sees in all weather," Jakobsdottir notes.

Still, satellites can complement ground-based measurements of volcanic gas emissions. NASA's EOS satellites carry UV spectrometers, and several research groups use these readings to assess volcanoes across the globe on an ongoing basis, though they lack the continuous coverage ground-based monitoring systems offer.

Vogfjörd believes such local gas monitoring is needed if Iceland is to better predict its explosive future. While the world's eyes are now on Eyjafjallajökull, and its even more dangerous neighbor Katla, she's making plans to install gas monitoring equipment on Hekla, which erupted in 1970, 1980, 1991, and most recently in 2000. "Multidisciplinary monitoring is the way to go because no one thing is going to show you what you need to know," she says.

—LUCAS LAURSEN

Lucas Laursen is a freelance writer based in Madrid.

Scary smells. The March eruption of Eyjafjallajökull brought scientists to measure volcanic gases.

PHOTO CREDIT (BOTTOM) COURTESY MICHAEL BURTON/ISTITUTO NAZIONALE DI GEOFISICA E VULCANOLOGIA, INGV

PALEOANTHROPOLOGY

Human Ancestor Caught in the Midst of a Makeover

ALBUQUERQUE, NEW MEXICO—Renowned paleoartist John Gurche prides himself on his accurate reconstructions of early humans. But last week, the famed human ancestor *Homo erectus* was giving him trouble. Gurche immortalized a female *H. erectus* in bronze for an exhibit that opened this month at the Smithsonian Institution's National Museum of Natural History, so he watched with some trepidation as the species got a new look at the annual meeting of the American Association of Physical Anthropologists here. Several talks and posters reported how new discoveries and analytical methods are altering views of this species, from the way it looked to how it grew up and gave birth. "This gives you a good idea how much our view of *H. erectus* is in flux," said Gurche.

By the time researchers were done, some early members of *H. erectus* had morphed from tall, slender-hipped individuals that looked a lot like us into shorter, broader hominins. "*Homo erectus* continues to evolve," says paleoanthropologist Scott Simpson of Case Western Reserve University in Cleveland, Ohio.

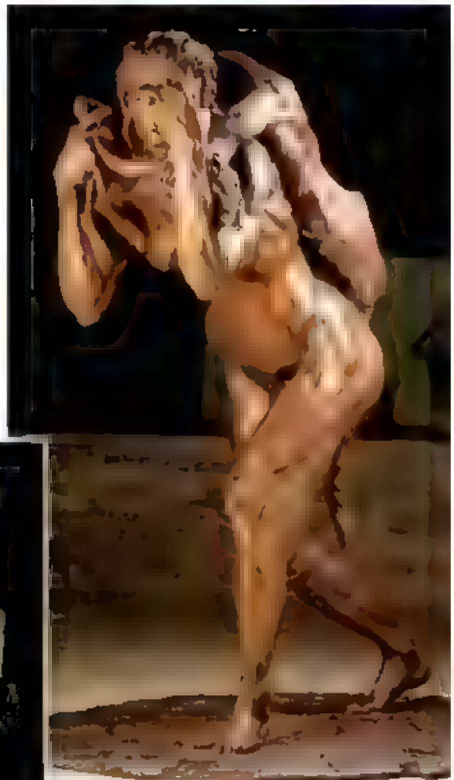
One individual—the rare partial skeleton of the Nariokotome Boy—has dominated views of *H. erectus* for nearly 2 decades. This adolescent died 1.6 million years ago near Lake Turkana in Kenya where he was discovered in 1984. Researchers thought this boy grew at the same rate as modern humans and initially calculated that he was about 11 to 12 years old when he died. If he had undergone an adolescent growth spurt, as we do, he would have reached a strapping 188 centimeters and 68 kilograms as an adult. Because there were no other complete pelvises of early *Homo*, researchers also used modern human proportions to put together the boy's pelvis. So it came out quite narrow, like ours, says paleoanthropologist Christopher Ruff of Johns Hopkins University in Baltimore, Maryland, who helped do the reconstructions.

This view of a lanky youth who looked modern from the neck down—there's no doubt that *H. erectus*'s brain was much smaller than ours—spurred many interpretations of the species's biology. For example, researchers suggested that its height was an adaptation to stay cool and to run efficiently in the hot tropical climate. The slender hips also gave the boy's female brethren a narrow birth canal, implying that newborns had small brains and were helpless at birth.

H. erectus has been brought down to size lately, though, as researchers have found several smaller individuals, including some outside Africa (*Science*, 21 September 2007, p. 1664); many suspect the species may have had more sexual dimorphism than had been thought, because *H. erectus* now appears in both short and tall sizes, based on long bones. New dental methods also predict that *H. erectus* grew faster than we do, at a rate closer to a chimpanzee's than to ours. Using intermediate growth rates, graduate student Ronda Graves of Stony Brook University in New York state calculated that Nariokotome Boy would have had less time than originally predicted to reach his adult height when he died. She estimated at the meeting that he would have reached 163 cm in height and 56 kg in weight as an adult—"shorter and wider" than previously thought.

Just how much wider was illustrated in another team's reconstructions of the boy's pelvis, also unveiled at the meeting. Simpson and Linda Spurlock of the Cleveland Museum of Natural History realigned the pieces of Nariokotome Boy's pelvis, guided by a female *H. erectus* pelvis from Gona, Ethiopia, that Simpson reported 2 years ago (*Science*, 14 November 2008, p. 1089). They found that the widest measure from side to side on the boy's pelvis is 255 to 260 millimeters rather than 225 to 230 mm. This would give the boy an adult hip breadth of 295 to 301 mm rather than the 266 mm originally proposed, and would match those of the short, wide-hipped female from Gona, whose pelvic breadth was 288 mm. "*H. erectus* was not simply a small-brained modern human," says Simpson.

Ruff agrees that the boy's height and pelvis need to be revised, but he thinks Graves and Simpson may have gone too far. Graves's numbers rely on "unrealistic" growth trajectories: Even if the boy grew as fast as a chimpanzee, he would have reached 175 cm and 75 kg as an adult, he says. Ruff also thinks Simpson relied too heavily on the Gona pelvis. That specimen was not found with other identifying bones, and it is so small-bodied that Ruff thinks it may have belonged to an australopithecine—a proposal that Simpson vigorously challenged in the question-and-answer period after Ruff's talk.



How tall? Reconstructions of *H. erectus*, like this female in bronze, are based in part on the Nariokotome Boy skeleton (*inset*).

If *H. erectus* was broad-beamed, the wider birth canals of females would allow their babies to be born in a more straightforward way than those of *H. sapiens*, which must rotate during birth so their heads can fit through a narrow birth canal, says paleoanthropologist Karen Rosenberg of the University of Delaware, Newark. That's "more reasonable," she says, and fits better with other extinct hominins.

The diverse meeting reports are just the most recent revisions to *H. erectus*, says Gurche, who could be found taking careful notes at every *H. erectus* talk. About 16 months ago, he was finishing up an *H. erectus* model when the wide-hipped Gona pelvis was published. So Gurche remodeled his statue to make the hips a centimeter wider. Four months later, he was putting the final touches on the cast when newly discovered footprints in Kenya suggested that *H. erectus* had shorter toes. "I had to chisel the toes," says Gurche. "We should lock these guys in a room together until they work *H. erectus* out."

–ANN GIBBONS

ECOLOGY

Along With Power, Questions Flow At Laos's New Dam

Easing the impact. Water released from the NT2 dam passes through a novel aeration weir (*above*) before it enters the Xe Bang Fai River

The start-up of one of Southeast Asia's biggest hydropower dams has launched a new round of debate over how much damage the megaproject might inflict on the environment.

Backers led by the World Bank and the Asian Development Bank (ADB) say that the $1.5 billion Nam Theun 2 (NT2) dam in central Laos has already taken its most severe toll on the environment: Filling the reservoir in 2008 involved resettling 6200 people and inundating 450 square kilometers of the Nakai Plateau. But critics say that the ecological harm has only just begun. "NT2 will lead to very serious impacts" for more than 100,000 people living downstream, says a U.S. expert on water issues in Laos who asked to remain anonymous out of fear of offending the Lao government. "World Bank and ADB will, I expect, regret ever getting involved in this project." Not so, says a World Bank official. "A thorough analysis of probable downstream impacts, as well as a credible and comprehensive mitigation and compensation program, was critical to getting the World Bank to support NT2," he says. Both sides agree that a major experiment in hydrology and ecology is now under way.

The project, run by the Nam Theun 2 Power Company (NTPC), diverts water from the Nam Theun River, a tributary of the Mekong River, into Nakai Reservoir, from which water is released via a 27-kilometer channel to another Mekong tributary, the Xe Bang Fai. The Lao government will plow its $2 billion share of revenue from electricity sales in the next 2 decades into a national fund for alleviating poverty. Other aspects of NT2 have gotten a thumbs-up from some experts, who stress the good it will do for the impoverished Nakai Plateau. The resettlement plan is "state of the art," says Thayer Scudder, an anthropologist at the California Institute of Technology in Pasadena who, with two colleagues, has served as an NT2 expert panel since 1997. Still, Scudder cau-

INTERNATIONALIZATION

Max Planck Tests the Korean Waters

In another sign of the Max Planck Society's desire to extend its reach beyond Germany, it is negotiating with Pohang University of Science and Technology (POSTECH) to establish two joint research centers there. The South Korean side would like to see the centers evolve into a full-fledged Max Planck Institute. But because of some hard-learned lessons, Max Planck is being cautious about its commitment, and officials warn that the deal is not finalized. "We need to make sure that when Max Planck is on the label outside, that it's really on the inside, too," says Berthold Neizert, head of the Max Planck Society's (MPG's) international division.

The matchmaker behind the growing ties between MPG and South Korea is theoretical physicist Peter Fulde, a former director of the Max Planck Institute for the Physics of Complex Systems in Dresden. In 2007, Fulde became a POSTECH professor and president of the Asia Pacific Center for Theoretical Physics (APCTP), housed on the POSTECH campus. At APCTP, Fulde helped establish an independent program for junior research groups co-sponsored by Max Planck. As visits increased between MPG and POSTECH, the parties agreed in January 2009 to study setting up the centers.

If cleared by MPG's scientific evaluation, which is expected to be completed in the next month, one of the centers would focus on attosecond spectroscopy, which uses lasers to study the dynamics of electrons. The other would add two new beamlines to a current $100 million upgrade to the Pohang Light Source to characterize and analyze new materials. POSTECH and MPG researchers are already cooperating in these areas, and "with the centers, there will be more of an impact," says Fulde.

Both sides see advantages. "What we like is the tremendous drive [in Korea]. There is so much potential there," says Neizert. "Korea is now trying to focus on creative research excellence, and this will be a very good opportunity for Korean groups to work hand in hand with top groups from Max Planck," says Kim Seunghwan, a POSTECH physicist involved in setting up the centers.

Kim says they expect that the two centers will eventually have 100 Ph.D.-level researchers, including up to 30 newly recruited junior scientists, and $30 million in funding over 5 years. Details have not been finalized. Neizert says budget questions are still under discussion, but funding would come from both partners.

POSTECH had hoped to create a full MPG institute, but MPG held back. Fulde says that although South Korean and German scientists cooperate very effectively in the lab, the two countries have different approaches to managing research. In South Korea, "funding is in little boxes, so to speak, and [authorities] look into each box," Fulde says. "In Germany, there is much more flexibility in the financing system."

Such differences have tripped up some of

CREDITS: PHOTOS BY VINCENT GAUTIER/NTPC

tions, "implementation is the name of the game, not planning."

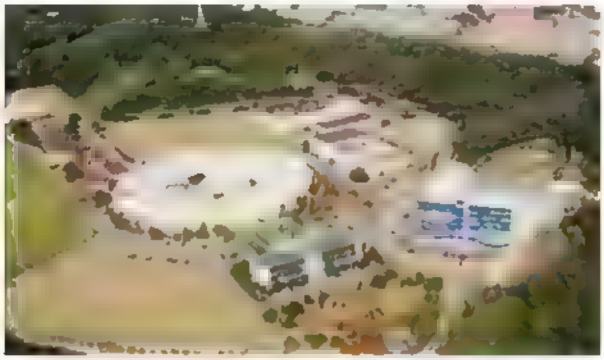
Tensions over NT2's environmental legacy have simmered for years. "Diverting a large amount of water from one river basin to another, via a large reservoir with deoxygenated and eutrophic water in it, will greatly change the hydrology and water quality of the Xe Bang Fai," says the U.S. expert, who predicts that erosion will also be a major problem. Mitigation measures, he insists, are insufficient.

When the dam began generating electricity and water flow changed last month, critics pounced. In a 26 March letter to the World Bank and ADB, the advocacy groups International Rivers and Mekong Watch asserted that water quality on the upper Xe Bang Fai deteriorated when river levels rose 3.6 meters. The groups claimed that the rapid rise had washed away gardens on the river's banks and that fish had "disappeared from the river." They also charged that NTPC has failed to provide adequate alternative drinking water supplies. "The project is violating people's human rights by preventing access to clean water and by destroying critical food sources without providing compensation," contends Ikuko Matsumoto, Lao program director for International Rivers. The letter called on the World Bank and ADB to suspend dam operation and strengthen downstream mitigation measures.

Such criticism is unwarranted, NT2 backers say. In an 8 April letter to International Rivers and Mekong Watch, the World Bank and ADB asserted that "considerable progress" has been made with the downstream mitigation and compensation program and that "effective erosion, water quality, fish catch, and socioeconomic monitoring systems" are in place. The letter notes that some 500 boreholes and pumps have been installed to provide drinking water, for example. Thanks in part to structures such as an aeration weir, "initial results show that water quality in the Xe Bang Fai is not significantly different to how it was prior to the project," says NTPC spokesperson Aiden Glendinning. "These results were shared with [International Rivers] before they made their claims of pollution and fish loss, for which no evidence has been found anywhere along the river," he says.

Work on NT2 has yielded one welcome surprise: a find of 38 large-antlered muntjacs, a rare deer, on the Nakai Plateau (*Science*, 4 September 2009, p. 1192). But with the electrical spigot now open, the question is whether NT2 will improve or worsen the welfare of communities downstream. On that count, the verdict on NT2 is not yet in.

–RICHARD STONE



New views. The Pohang Light Source may play host to a joint research center being discussed by the Max Planck Society and Pohang University of Science and Technology.

CREDIT: POHANG ACCELERATOR LABORATORY

Max Planck's previous international endeavors, such as the Partner Institute for Computational Biology in Shanghai, a joint venture with the Chinese Academy of Sciences (*Science*, 9 November 2007, p. 902). After a rocky start, most of the management issues have now been smoothed out. "Shanghai is running really well, and the science is absolutely tops," says Neizert. "But at the same time, we had to invest so much time and energy to make sure [the Max Planck] label fit."

Neizert says that label means that no matter where in the world a Max Planck institute is located, "the governance needs to be like it is in Germany, with the scientific directors having full independence and long-term financial security." Max Planck and POSTECH did discuss the idea of an institute. "But we felt it was simply premature," Neizert says. Kim says they have agreed to evaluate results of this Max Planck Korea Initiative in 5 years.

Korea is the latest example of MPG's push for international cooperation. The Max Planck Florida Institute in Jupiter opened in 2009, and a Max Planck Center focused on computer science was inaugurated in India in February. "Internationalization has been a central issue for [Max Planck president] Peter Gruss," Neizert says. The society is in talks about similar collaborations with institutes and universities in at least three other countries.

–DENNIS NORMILE AND GRETCHEN VOGEL

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*Science*Insider

From the *Science* Policy Blog

The U.S. Department of the Interior, which sells the oil and gas leases on the outer continental shelf, announced that the U.S. Geological Survey would carry out a scientific review of **drilling in the Chukchi Sea** by 1 October. http://bit.ly/bbLC3h

The Climatic Research Unit at the University of East Anglia in the United Kingdom has been **cleared of charges of scientific "impropriety"** by an independent review headed by former geologist Ronald Oxburgh. The review, which looked at the behavior of scientists in the context of so-called Climategate, said that the scientists should improve their statistical methods. http://bit.ly/c2fblu

WiCell, a nonprofit at the University of Wisconsin, Madison, has asked the National Institutes of Health (NIH) to add four key lines to a **registry of stem cell lines** eligible for federal funding. NIH must first ensure that the lines comply with ethical guidelines. http://bit.ly/aErcAB

A U.S. House of Representatives panel has defined high-risk research and specified that the National Science Foundation should spend at least 5% of its research funds on such work. The definition is part of a planned reauthorization of the **America COMPETES Act**, which covers programs at several science agencies. http://bit.ly/chLsCc

Russian Prime Minister Vladimir Putin has announced **$1.3 billion in fresh funding** for new universities, research grants, and infrastructure. The focus, he said, is on applied work that would impact Russia's "real economy," worrying scientists who say that fundamental research has been neglected. http://bit.ly/cgMVzu

Controversial AIDS scientist **Peter Duesberg is being investigated for fraud** by his university, the University of California, Berkeley. The charges stem from a paper he and four colleagues published last year in *Medical Hypotheses* that was later withdrawn by Elsevier. http://bit.ly/aiRzo7

For the full posts and more, visit **news.sciencemag.org/scienceinsider**.

U.S. GEOLOGICAL SURVEY

Pioneering Geophysicist Tackles Newest Challenge

More ink? Marcia McNutt wants to increase the visibility of the venerable U.S. Geological Survey.

Marcia McNutt oversees what she likes to call "the nation's only integrated natural science agency." Whether it's estimating how much natural gas awaits discovery in the eastern Mediterranean, figuring out why mixed-gender fish are showing up in the Potomac River, or calculating the odds of a sleeping Cascades volcano spouting off, the 4400 biologists, geologists, hydrologists, and mappers who work at the U.S. Geological Survey (USGS) have a hand in it. Its supporters say that, for just over $1 billion a year, USGS may also be the nation's biggest scientific bargain.

The survey's "science capacity is just too small," says Craig Schiffries of the Washington, D.C., office of the Geological Society of America. "Marcia McNutt has the capability to elevate the profile of the Geological Survey within the Department of the Interior (DOI) and beyond. She's not one to sit on the sideline."

Indeed, McNutt, 58, has been a pioneer throughout her career: The first female physics major at Colorado College, first female lifeguard for the city of Minneapolis, and the first woman to train in underwater demolition with Navy SEALs. In 2005, the geophysicist was elected to the U.S. National Academy of Sciences. Last fall, after 12 years as president and CEO of the Monterey Bay Aquarium Research Institute (MBARI) in northern California, she became the first woman to lead the 131-year-old survey. She's also the first director to be science adviser to her boss, Interior Secretary Ken Salazar

The survey's profile has been so low, says former acting director P. Patrick Leahy, now executive director of the American Geologic Institute in Alexandria, Virginia, that people around DOI would often ask, "What does [it] do?" One answer, McNutt says, is finding "defensible solutions" to problems encountered on the 20% of U.S. land area that DOI manages through its agencies, which include the National Park Service and the Bureau of Land Management. But the survey's role extends beyond public lands across the range of its expertise, from assessing U.S. water resources to the aftermath of the Haiti earthquake.

Despite its crucial roles, "the USGS as an agency had been barely treading water for many decades in terms of its budget," McNutt told *Science* in a 29 March interview. "There's this discrepancy between the science agencies, like NASA and NSF, that are independent, versus the ones inside of Cabinet-level departments [like USGS] in terms of their freedom to raise their own profiles. I'm not sure past [DOI] secretaries have even noticed there was a USGS," McNutt says.

That's no longer the case, she asserts. "We do have a secretary who thinks of science first in terms of decision-making, who really wants the USGS to prosper," she says. "We have an obligation and an opportunity to take advantage of that to try to raise the visibility of the USGS."

Being science adviser, a position that she suggested Salazar create for her, is one such opportunity. "Sitting around the table at DOI," she says, "I will be the only scientist with a number of lawyers. So my job is to interpret science to a group of people who really care about using science but [who] may not be professional scientists."

McNutt feels that her status, combined with management experience she gained at the 200-employee MBARI, will help her garner attention well beyond DOI. "When Secretary Salazar goes to other agencies about science advice from the Geological Survey and he mentions my name, it gets respect" from heads of other science agencies who know her, she says. "Most of my job is really focused on satisfying what is almost an insatiable demand for scientific information."

At the same time, McNutt recognizes that a trillion-dollar federal budget deficit may thwart any plans for short-term, rapid growth of the survey's own budget. So she's looking to expand partnerships with other federal agencies and other groups. One very preliminary idea would use the survey's seismometers to provide an early-warning component in an ocean-observatories network that the National Science Foundation is building on the sea floor on the Pacific Northwest coast. More partnerships might also broaden the survey's base of support, guesses former survey director Charles Groat, now at the University of Texas, Austin. "The survey doesn't give out a lot of money," he notes, which limits the constituencies that will defend its budget.

Internally, McNutt has discussed the idea of reorganizing the survey to reflect the six "science directions" in its 10-year strategic plan.* Such a reorganization would create divisions for hot-topic areas such as climate variability, the role of the environment and wildlife in human health, and a water census. They would replace current disciplinary compartments such as biology, geography, and geology.

The subject of reorganization was taken off the table for this interview, but it's already created a buzz within the survey. "That would certainly be a shock to people in the Geological Survey," Groat says. "I'm not sure I'd try it, [but] Marcia's gutsy."

–RICHARD A. KERR

*pubs.usgs.gov/fs/2008/3008

CREDIT: U.S. GEOLOGICAL SURVEY

REGULATORY POLICY

Congress Moves Toward Strengthening EPA's Hand on Chemical Safety

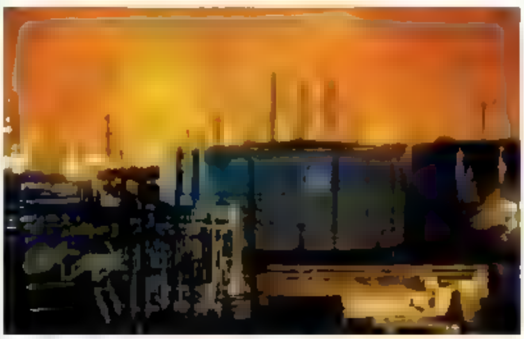
The U.S. Environmental Protection Agency (EPA) is responsible for regulating more than 80,000 industrial chemicals, but for more than 30 years it's been hamstrung in its ability to demand lab tests and safety data from companies. Now two bills in Congress would change that.

If passed, the bills would require chemical companies to provide much more safety data to EPA. The proposed legislation also expands EPA's role in determining safety, which some say could drive advances in toxicological research. "This is a monumental sea change," says Richard Denison of the Environmental Defense Fund in Washington, D.C.

Many important details remain to be worked out. But with support in principle from both environmentalists and chemical industry trade groups, the effort to reform chemical-safety analysis appears to have considerable momentum.

Industrial chemicals in the United States are regulated under the Toxic Substances Control Act, which has not been updated since it was passed in 1976. Under the existing system, for example, EPA must prove that chemicals pose an unreasonable risk before it can demand additional data from companies.

Last week, Senator Frank Lautenberg (D–NJ) introduced a bill that would require companies to provide EPA with a minimum set of data on existing and new chemicals so that EPA can assess the safety of all industrial chemicals within 15 years. That's a huge task, experts say. Risk assessments are expensive and often take years. "I have no clue how the agency is going to do safety standards on tens of thousands of chemicals in 15 years," says Joel Tickner of the University of Massachusetts, Lowell.



Shedding light. Chemical manufacturers would have to submit more safety data to EPA.

CREDITS (TOP TO BOTTOM): NASA/JPL-CALTECH; PHOTOS.COM

Because of the size of the challenge, the bill directs EPA to prioritize and create a running list of the 300 potentially riskiest chemicals, such as those that bioaccumulate. When a chemical is added to the list, companies would have 18 months to provide data. If warranted, EPA would retain the authority to ban or restrict a chemical.

The bill sets the standard of safety as a "negligible risk of any adverse effect," but exactly what that means is open to interpretation. EPA would be required to calculate the aggregate exposure to a chemical from all routes, such as from eating food and breathing dust. That's going to be complicated for industrial chemicals, which can be used in thousands of products.

An even larger challenge would be the mandate to gauge the cumulative effect of various chemicals. EPA has spent years figuring out how to analyze the combined risk from exposure to pesticides, lumping them by mode of action. Industrial chemicals pose a much harder problem because less is known about how they might affect organisms. "It's almost technically impossible," says toxicologist Richard Becker of the American Chemistry Council in Arlington, Virginia.

Another crucial question is what kind of "adverse effect" should be used as a sign of a health hazard. Typically, EPA considers endpoints such as cancer in a lab animal, but the bill would give EPA the authority to expand its definitions to include biochemical changes, such as those detected in highly automated cellular tests. "You're ramping the law up to modern 21st century toxicology," says Paul Locke of Johns Hopkins University in Baltimore, Maryland. But Becker says that few such biochemical markers are ready for application; often it's not clear what these subtle changes mean for human health.

Representative Henry Waxman (D–CA), who heads the House Energy and Commerce Committee, released a similar draft bill last week and intends to hold hearings in June or July. But with fewer than 90 working days left for Congress, the bills may not pass this session. That's not necessarily a bad thing, say Tickner and others, as it may allow time for important questions to be resolved. **–ERIK STOKSTAD**

ScienceNOW

From *Science's* Online Daily News Site

Good Dogs Live Longer
Small dogs generally live longer than big dogs—so that yappy Yorkshire terrier next door could be around for a long time. But body size isn't the only factor that determines how long dogs survive. Personality influences life span, too, according to a new study that might help explain how animal dispositions evolve. http://bit.ly/gooddogs

Mystery of the Zodiacal Light Solved
Zodiacal light—the faint white glow that stretches across the darkest skies, tracing the same path the sun takes—has mystified scientists for centuries. They've known that it is sunlight reflected from a disk of dust spanning the inner solar system from Mercury to Jupiter. They just didn't know where the dust came from—until now. http://bit.ly/zodiacal-light

Frostbite? Not for these Microbes
With a splash of a particular chemical solution, microbes can survive in large numbers at temperatures as low as −80°C, researchers report. Because similar chemical cocktails exist on the cold surfaces of Mars, the moon, and Europa, the findings may increase the chances of finding life on other worlds. http://bit.ly/coldmicrobes

Quantum Cryptography Hits the Fast Lane
Whether for online bills or military secrets, encryption schemes help keep digital communication secure. In recent years, physicists and engineers have been developing methods that transmit uncrackable encoded messages in individual particles of light, or photons. Now, one team has taken such quantum cryptography a long step forward by demonstrating a system that's fast enough to encrypt a video transmission. http://bit.ly/quantumcryptography

Read the full postings, comments, and more at **news.sciencemag.org/sciencenow.**

A Groundbreaking Observatory To Monitor the Environment

A decade in the making, the National Ecological Observatory Network (NEON) hopes to set a new standard for tracking long-term ecological change across the United States

The wild side. Niwot Ridge is one of 20 "wildlands" spots slated to be part of NEON.

CREDIT: E. PENNISI/SCIENCE

BOULDER, COLORADO—Plowing a path through 43 centimeters of freshly fallen snow in late March, the snowcat rumbles past the last spruces and climbs up above the tree line of Niwot Ridge, elevation 3300 meters. Its driver, hydrologist Mark Williams of the University of Colorado, Boulder, is accompanying the area's climatologist on his semiweekly trek to check instruments and change out equipment for experiments, some of which have been running for decades.

A field site since 1951 for what is now the university's Institute of Arctic and Alpine Research, Niwot Ridge has provided researchers with a unique opportunity to witness the interaction of climate—snow, rain, wind with the local soil, flora, and fauna. Among other advances, the work has helped explain the role that snowbound microbes play in the nitrogen cycle. The equipment is not much to look at: a few rows of snow poles, a couple of antennas with instruments mounted on their booms, and an odd-looking, two-bucket setup for collecting rain and snow. And the mode of research is time-tested: Individual researchers design and set up their experiments, often on a shoestring budget, and then visit them periodically to collect data that are shared with the community and that inform the next set of experiments.

But that small-scale, incremental approach to science is about to change. A 20-meter-square patch of land here is slated to be one of 20 sites in a $434 million project funded by the National Science Foundation (NSF) that will usher in a new era of large-scale environmental science. The project, called the National Ecological Observatory Network (NEON), represents the most ambitious U.S. attempt to assess environmental change on a continental scale.

Next month, NSF's oversight body, the National Science Board, is expected to give its final approval to NEON, and NSF has requested $20 million in its 2011 budget to begin construction. Within 5 years, if all goes well, an 8-meter steel tower will dominate this landscape, bearing instruments that will make it possible to compare this environment with 19 other ecosystems across the country. "This is an entirely new resource for ecology," says Michael Keller, chief of science at NEON Inc., the nonprofit consortium that runs NEON. Christopher Field, an ecologist at the Carnegie Institution for Science in Stanford, California, expects NEON "to produce some fundamentally transformational results."

Online
sciencemag.org
Podcast interview with author Elizabeth Pennisi

For NEON to do that, however, ecologists will need to change how they do science. Instead of being free agents deciding what data they will collect, how, and from where, the researchers will need to become part of a collective, tapping into a database whose parameters have already been determined in a top-down approach. They will need to practice "ecoinformatics": the use of computers and software tools to integrate different types of information from many locations. They will need to think about trends across a whole country instead of a single ecosystem. The success of NEON will depend in large part on whether they embrace or reject that new model.

Not everyone is pleased with how the project is set up. Some, like ecologist David Tilman of the University of Minnesota, Twin Cities, lament the excision of an experiment to test the effects of global change. They say such an experiment, deemed too expensive, is essential to obtaining timely answers about climate change. Others complain that NEON won't be investing enough in the field sites that will host its instruments. There's also some concern that ecologists, untrained in the approach NEON is taking, won't use NEON's data. "Everybody still has some questions because it's a new thing," says John Porter, an ecologist at the University of Virginia in Charlottesville who is not part of NEON.

LTER on steroids

Monitoring a patch of land over time isn't a new idea for NSF. In 1980, it set up five U.S. sites, including one at Niwot Ridge, under the Long Term Ecological Research (LTER) Network that has grown to 26 sites, including

two in Antarctica and one off the Fiji Islands in the South Pacific. The $30-million-a-year program is widely considered a success, with findings on the effect of global warming on plant diversity, how forests could be overloaded by anthropogenic nitrogen, and the greater stability of diverse ecosystems.

But by the late 1990s, says Williams, "we realized there were limits to the LTER model." Each LTER was designed to answer questions posed by an individual investigator or a small team. Core activities, such as measuring primary productivity, were not a high priority, Williams acknowledges. "It was hard to integrate data [from different sites] and to do synthesis," he adds, because investigators followed different timetables and used different instruments.

At about the same time, Williams says, the community began to ask itself, "How do we grow ecology, and how do we tap additional resources?" For NSF program managers, the goal was to fund construction of a large-scale biology project without devouring their annual budgets, which nurture thousands of individual investigators (*Science*, 20 June 2003, p. 1869). Their models were the astronomy and geosciences communities, which have managed for decades to build costly instruments such as telescopes and ships without bankrupting their bread-and-butter programs. NSF already had a mechanism: Its budget included a special facilities account to finance construction of half a dozen projects at a time, with the understanding that NSF's research directorates would pay for operations and maintenance of those facilities from their annual budgets.

A series of workshops yielded a vision of NEON hailed by then-newly arrived NSF Director Rita Colwell, who inserted the project into NSF's 2001 budget request to Congress. But the larger ecological community had reservations. Congress also balked, wondering what particular scientific question NEON would be addressing.

In response to that resistance, NSF asked the American Institute of Biological Sciences to hold three town meetings in 2002 and 2003. The resulting white paper called for a network of 17 sites in different biomes that, in turn, would be linked to other research sites nearby. Each site was projected to cost $20 million to set up and $3 million a year to operate.

Again, however, the community was divided. Although some people were excited, others wondered if ecologists, known for being independent, would take full advantage of NEON. To many, the program looked like "LTER on steroids," says Williams. "It was not a good-enough plan."

The united domains of America. Scientists divided the United States into 20 ecological domains. Three sites within each domain will be instrumented.

SOURCE: NEON

Next up was an evaluation by the U.S. National Academies. The resulting National Research Council (NRC) report endorsed NEON in principle but urged that the program be reoriented around six specific research questions, including biodiversity and land use. Each question would be the focus of one observatory (*Science*, 26 September 2003, p. 1828). "It forced us to look at large-scale ecological processes and large-scale drivers of change," says NSF's Elizabeth Blood. Nonetheless, Congress chose not to give NSF money in 2004 to begin construction, the third time in 4 years it had passed on funding NEON.

A plan takes shape

For NSF, the flaw in the NRC proposal was that the observatories were too independent to be considered a single entity. That feature would preclude NEON from being funded by the agency's major research equipment account. For NEON's supporters, the solution was obvious. NEON "must be built as one giant Earth-facing telescope," says David Schimel, CEO of NEON Inc. Although there would be multiple sites, together they would cover the entire nation in a statistically valid way. "It really is taking a different approach to doing national-level science," says Porter.

The first step was to refine the six research questions as science goals that could be tackled on a continental scale. Next came deciding what measurements would address these goals. NEON "needed to come up with those things that can be measured in the same way in every place," Porter recalls. Only with uniform, standardized data would researchers be able to "statistically integrate the information to look at processes at a bigger scale," explains Blood.

Coming up with what biology to monitor, for example, was a challenge because each site has a distinct assortment of plants and animals. NEON's designers settled on a few key groups. Bypassing ants and frogs, they chose beetles, mosquitoes, birds, deer mice, and microbes. The last will be characterized by DNA sequencing. The team also had to develop a plant-sampling procedure that could work in grasslands as well as in a forest.

Every site will have a tower that reaches about 10 meters above the existing vegetation. Each tower will host instruments for measuring climate variables such as temperature and wind speed as well as the exchange of carbon dioxide between the atmosphere and the land and vegetation in the immediate vicinity. NEON also plans to measure soil carbon dioxide and other soil characteristics, and will use fiber optic video cameras, called minirhizotrons, to monitor root growth. "What is unique and revolutionary is the fact that [these instruments] are being deployed all over the country," says Field.

Three airplanes will be equipped with a spectrometer that detects "greenness" of the vegetation by picking up the chemical fingerprints of the area they fly over. Those data can be matched with satellite observations to look for changes in vegetation and land use. The

Test bed. All NEON sites will have a tower like this prototype, which is used for evaluating sensors, communications, and data [illegible]

planes will also carry cameras and lidar to measure forest canopy heights and biomass.

Initial plans for a giant climate change experiment that would manipulate carbon dioxide and temperature locally were dropped after the approach proved to be too expensive and unwieldy. However, a smaller manipulation survived as part of an effort to build predictive models of how streams adapt to stress. The Stream Observatory Network Experiment will boost nitrogen and phosphorus levels in 10 streams and monitor the impact for at least a decade. Upstream traps will also remove fish and other organisms at the top of the food chain, mimicking one of the big threats to aquatic ecosystems worldwide.

All together, NEON's instruments and people will monitor 550 variables, and the data will be released to the public after being checked for quality. In many cases, NEON will also provide analyses that incorporate spatial and temporal information, and use models that predict parameters, such as net productivity, that couldn't be measured directly.

While some scientists were debating what to monitor, others began figuring out how to divide up the country. "We wanted to maximize the amount of environmental variety in North America," says Schimel. William Hargrove, now with the U.S. Forest Service in Asheville, North Carolina, created a matrix for each square kilometer of the United States with data on nine variables, such as days below freezing, amount of precipitation in the growing season, and vegetation growth. Using a supercomputer, he grouped like squares to come up with specific regions, called domains, characterized by particular ecological characteristics: tundra, prairie, alpine, and southeastern forest domains, for example. After settling on 20 domains, Hargrove and his colleagues then determined which locations in each domain best represented the range of environmental conditions of that domain.

Each domain will have one permanent "wildlands" site and two temporary sites that will host instruments for 3 to 5 years. Some 800 permanent sites were proposed; under the rules, a potential site needed to be available for 30 years, offer year-round access, and permit flyovers by remote-sensing aircraft. To reduce the cost of visits, the sites within a domain also needed to be as close together as possible.

Full speed ahead?

The site selection was completed in 2007, and in November 2009, NSF signed off on NEON's final design. If approved by the science board, NEON expects to start work this summer at an agricultural field in eastern Colorado, followed in summer 2011 by the core site of that region in the Central Plains Experimental Range, 241 kilometers away. It hopes to build sites at two domains in the first and final years of construction, and four a year over the middle 4 years. NSF is asking Congress for $20 million in FY 2011 in a budget that ramps up to about $100 million annually in 2013 and 2014; work on all 20 domains should be completed in 6 years. Niwot Ridge will be one of the last sites built. NEON's annual operating budget is expected to be $80 million.

But will this be money well spent? Not everyone thinks so. "I don't believe we will move environmental science along at the maximum speed with NEON," says William Schlesinger, a biogeochemist at the Cary Institute of Ecosystem Studies in Millbrook, New York. "I think if you took the same amount of money and used it to enhance the competitive grants for young people, we'd get [better] science for the money."

Tilman, the chair of the NRC committee that reviewed NEON in 2003, also has some reservations. "The current NEON in my mind takes too literally the word 'observatory,' " he says. He disagrees with NEON's decision to drop the climate change experiment his panel recommended. "You need observations of natural systems and observations of experimentally manipulated systems" to begin to determine cause and effects and then to check those findings against what is happening in nature, he says. Those experiments would also motivate young researchers to invest their careers in NEON, he adds.

Indeed, there's an undercurrent of nervousness about whether the community will use the information that NEON generates. "People are a little wary about what we'll get out of it," says Eugene Kelly, a soil scientist at Colorado State University, Fort Collins. He thinks his generation of senior researchers might not benefit much from NEON because it has a different mindset, and many may not want to wait a decade or longer for the trends from the data being collected to become evident.

In addition, he and Williams are upset because NEON's investment in infrastructure at its sites, including places like Niwot Ridge, won't enhance existing facilities. "The sites get nothing" to augment their budgets, says Williams. "It's a major bone of contention." Williams worries that NEON will not be well integrated with the operations of his LTER once construction begins and that the two teams won't work together in a scientifically productive way.

But Schimel says NEON will pay its way at these sites and will work with local managers. And NSF is hoping to attract researchers with a new $20 million grant program announced this month. Macrosystems Biology: Research on Biological Systems at Regional to Continental Scales will fund proposals from scientists seeking to use data from NEON. Williams is already planning to apply for funds to incorporate early Niwot Ridge data into the NEON data stream.

"When they did the first [telescope] observatory, I bet it wasn't the very best there is," Porter explains. "But you will never get to that second observatory until you've had the first. We'll learn a lot from NEON."

–ELIZABETH PENNISI

CREDIT: NEON

NEWSMAKER INTERVIEW

Imponderables Complicate Hunt For Intelligent Life Beyond Earth

Those looking for signals from extraterrestrial civilizations should cast a bigger net, says Paul Davies, head of a group figuring out what to do if the search succeeds

The Search for Extraterrestrial Intelligence (SETI) leaped from fantasy to science 50 years ago this month when astronomer Frank Drake pointed the 26-meter telescope at the U.S. National Radio Astronomy Observatory in Green Bank, West Virginia, at a star 11 light-years away. Since then, astronomers have searched a few thousand stars in the hope of detecting radio messages from alien civilizations that might be living on planets orbiting them. Yet all the searches can attest to so far is the limitless optimism of SETI researchers.

In his new book *The Eerie Silence*, physicist **Paul Davies** argues for widening the search from radio messages beamed at Earth to beacons sweeping the galaxy, alien probes traveling through the solar system, and signs that viral DNA dispatched by a faraway civilization may have since become incorporated into the DNA of organisms on our planet. A professor at Arizona State University, Tempe, who serves as chair of the SETI Post-Detection Taskgroup, Davies spoke to *Science* recently about the past and future of SETI. His remarks have been edited for brevity.

–YUDHIJIT BHATTACHARJEE

Q: Why is the search for extraterrestrial intelligence any different from the search for goblins or unicorns?

P.D.: Good point. Well, when it started out 50 years ago, it was considered a very quixotic enterprise. The pendulum has swung during my career. I often ask around why it is now okay to talk about ET when it wasn't 40 years ago. And people will often cite irrelevant factors like—oh, we've discovered all these planets, and we've discovered that life can exist in a wide array of conditions. But the truth is that we still don't have an acceptable theory of life's origins, we really have no idea whether it was a stupendous fluke that happened only once or whether it pops up all over the place. It's now fashionable to say that the universe is teeming with life, but there is not a shred of evidence.

Q: The premise of "it's there but we haven't found it" sounds a bit like the claim of weapons of mass destruction in Iraq. To borrow from Donald Rumsfeld, the former U.S. defense secretary, doesn't ET belong in the category of "unknown unknowns"?

P.D.: It certainly does. To quote Jill Tarter [director of the Center for SETI Research in Mountain View, California], it's a hypothesis to be tested, and the way to test it is to go look. It's clearly not a logical absurdity that there exist other intelligent beings in the universe. But we really don't know what to look for; we only have the vaguest idea how to look.

Don't wait up. Davies's new book says ET probably won't phone us.

CREDIT: WIKIPEDIA

Q: What's the problem with the traditional approach to SETI: looking for radio messages targeted at us from a faraway source?

P.D.: It's just a speed-of-light issue. If you take Frank Drake's estimate of 10,000 civilizations in the galaxy, that places the nearest one 1000 light-years away. So they see us as we were 1000 years ago, [yet] it would make no sense for them to start transmitting until they knew we had radio technology. So the search in radio is fine, but expecting a message crafted for mankind deliberately directed at Earth beamed at us by an altruistic civilization that has no idea whether we'd pick up the message makes no sense. That's why I think we should shift the emphasis to searching for beacons, which are not directed at anybody in particular.

Q: How do you propose to widen the search?

P.D.: What we're really looking for is technology and its footprint. If we go with the hypothesis that in the distant past, some sort of alien expedition passed through the solar system, would anything at all remain of their presence? There are a few things: nuclear waste, genomes, major quarrying, or mining exercises—we might see traces of that. We need to think creatively how messages might be left for posterity, how technology might impact its environment either deliberately or inadvertently.

Q: Is it limiting to assume an ET that is interested in making contact with us?

P.D.: It is indeed. It also carries the hidden assumption of altruism, that they would do the heavy lifting [to signal to us]. We should shift the emphasis away from their deliberately getting our attention to—well, they're going about their business, how might we be able to detect that business?

Q: Would SETI have been worth it even if the conclusion is that we are alone in the universe?

P.D.: Well, absence of evidence isn't evidence of absence, so I don't think we'll ever know for certain. But if we did, then we might be much more inclined to take better care of our planet, to ensure the longevity of humanity, because if this alone is the spark of reason on this one pale blue dot, then we have an awesome responsibility to make sure it's not snuffed out. But personally I feel a lot more comfortable with the opposite conclusion: that the universe is intrinsically bio-friendly and that we are but one representative of a deep life principle that is built into the scheme of things. But that's just the romantic Paul Davies talking.

Q: You devote a chapter in the book to how governments, the media, and societies need to handle news of the detection of extraterrestrial intelligence, if and when that happens. What are the outlines of the plan?

P.D.: If there's a signal, the scientists should be allowed to evaluate it before there's a hullabaloo. In practice, that will be very hard to achieve without a cloak of secrecy, which I am usually against. But there's one thing on which we are all agreed, which is that we should not disclose the coordinates in the sky of a transmitting source. Because otherwise, any self-appointed spokesperson of humanity could get hold of a radio telescope and start beaming crackpot messages, and present themselves as a spokesperson for mankind, when it is not at all clear whether we should respond.

Up in smoke. China's tobacco use, increasing among women, causes a million deaths a year.

PUBLIC HEALTH

A Sense of Crisis as China Confronts Ailments of Affluence

As rates of behavior-related diseases rise, China's medical community looks for ways to change attitudes and advance preventive care

China is a land of superlatives: It consumes the most concrete and steel, emits the most greenhouse gases, and now, to the chagrin of health specialists, it has more people with type 2 diabetes than any other country in the world. By testing more than 46,000 people, Yang Wenying, a diabetes specialist at the China-Japan Friendship Hospital in Beijing, and colleagues extrapolate that 92.4 million Chinese—nearly 10% of the adult population—have type 2 (formerly "adult-onset") diabetes and another 148.2 million have prediabetes, or abnormally high blood sugar levels believed to presage the disease. Diabetes "has reached epidemic proportions," they concluded in a report last month in *The New England Journal of Medicine* (*NEJM*).

China's growing affluence is driving sharp increases in what were once considered scourges of the Western world: lung and breast cancer, obesity, diabetes, hypertension, and cerebro- and cardiovascular diseases. A rapidly changing lifestyle appears to be to blame, as Chinese are smoking more; consuming more fat, sugar, salt, and refined grains; and leading increasingly sedentary lives, particularly in cities and booming coastal regions. Somehow, most Chinese have not grasped that "as lifestyles change, diseases change," says Hao Xishan, president of Tianjin Medical University and chair of the Chinese Anti-Cancer Association. Ignorance and a health care system focused on infectious diseases have left China "facing a huge pending burden" from behavior-driven illnesses that are likely to take "a larger toll in the years to come," says Jeffrey Koplan, an epidemiologist at Emory University in Atlanta who works with Chinese colleagues on chronic-disease mitigation.

Fledgling efforts to retrain doctors to handle lifestyle diseases early and to raise awareness about disease prevention "need to be massively accelerated" for China to stave off a crisis, says Lincoln Chen, a public health scientist at China Medical Board, a foundation based in Cambridge, Massachusetts. "The whole of society should be mobilized to control noncommunicable diseases," says Yang Gonghuan, a deputy director of the Chinese Center for Disease Control and Prevention (CDC) in Beijing. A health reform plan adopted in April 2009 calls for attention to a number of noncommunicable diseases, but it doesn't go far enough, Yang says.

What's your brand?

For decades, China sought to vanquish diseases of deprivation, not excess. From 1973 to 2005, rates of infectious diseases and maternal and infant mortality dropped from 27.8% of all deaths to 5.2%, Yang and colleagues reported in the 8 November 2008 issue of *The Lancet*. Over the same period, noncommunicable diseases such as cancer, heart disease, and stroke rose from 41.7% to 74.1% all deaths (see chart, p. 423).

To Hao and others, the most frustrating aspect of China's noncommunicable disease problem is the country's stubborn tobacco habit. China manufactures an astounding 2.2 trillion cigarettes each year, making it by far the world's largest producer and consumer of cigarettes, according to Tobacco Atlas. Nearly 60% of Chinese men and 4% of women smoke regularly, reports the Chinese CDC. The World Health Organization estimates that smoking causes 1 million deaths a year in China.

Clever marketing of hundreds of brands selling at prices ranging from 14 cents to $33 per pack has made a person's choice of cigarette a sign of economic status, says Xiao Shuiyuan, a psychiatrist at Central South University in Changsha. "When men interact today, strong pressure exists for each to flaunt his preferred brand and 'courteously' exchange cigarettes, creating cycles of reciprocity that fuel nicotine addiction and impede quitting," Xiao and Matthew Kohrman of Stanford University in Palo Alto, California, wrote in the 8 November 2008 issue of *The Lancet*.

Cultural taboos have limited smoking among Chinese women, Xiao says, but attitudes are changing. In a small but telling survey at their university, psychologist Qi Yulong and epidemiologist Mei Cuizhu of Bengbu Medical College found that although only 4.9% of female students smoked, smoking was more prevalent among women from urban areas. City girls "were significantly more likely to think that a young woman who smoked was cool, mature, and charming," they reported last July in the *Journal of Nanjing Medical University*. A separate survey found that roughly one-fifth of female students aged 14 to 24 years had tried smoking. It is "an ominous harbinger" of future disease in a previously unaffected population, Thomas Novotny, a medical epidemiologist at San Diego State University in California, and colleagues asserted in a 2009 online article in *Tobacco Control*.

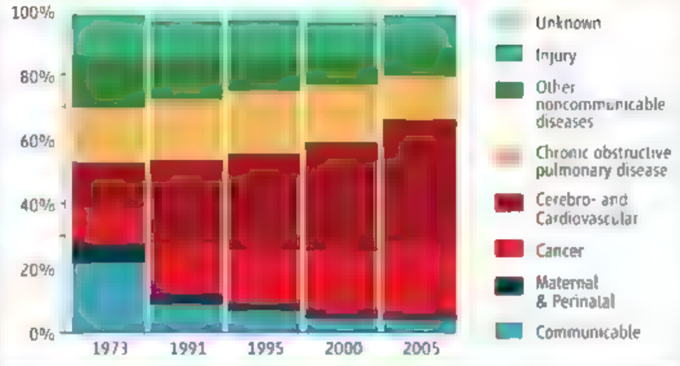
Tobacco companies target young women with slim, fashionably packaged cigarettes. Novotny and his group report that women believe these "feminine" cigarettes to be less harmful than regular brands. And the Bengbu study found that fewer than 45% of those medical university students were fully aware of the health effects of smoking.

One glimmer of hope, Xiao says, is that some municipalities have banned smoking in public places. Most notable is Beijing's pledge to make the 2008 Summer Olympics smoke-free. The city forbade smoking in taxis, sports arenas, museums, government buildings, and parks. These and other restrictions have remained in effect, says Xiao. Shanghai is now following suit by crafting an antismoking effort around the 2010 World Expo, which opens 1 May. Such restrictions have won broad support among educated professionals in China's eastern cities, Xiao says. "The culture is slowly changing, and this is really the best hope for controlling tobacco use in China," he says.

That enlightenment hasn't penetrated far into China's heartland. In Changsha, the capital of south-central Hunan Province where Xiao lives, "everybody still smokes," he says. And nationwide, cigarette sales are increasing. Hao believes the government should slap heavy taxes on cigarettes and funnel the proceeds to health research, but he doesn't see that happening any time soon.

Although some Chinese cities may be turning the corner on smoking, another deadly threat is gathering momentum. Breast cancer has become the most commonly diagnosed cancer among women in Beijing, Shanghai, and several other major urban areas, says Hao. Overall, breast cancer incidence in China is about one-third the incidence in the United States, he says. But that masks a startling discrepancy between rural areas, where the disease is still rare, and big cities—perhaps because of differing diets, Hao says. Shanghai, for example, in 2004 had 71 cases of breast cancer per 100,000 women. (The incidence among white U.S. women is about 128 per 100,000.) Mortality rates for breast cancer in China's cities rose 39% between 1991 and 2000, the biggest increase of any type of cancer, Hao says.

CAUSES OF DEATH OVER TIME



Ebb and flow. China has brought infectious diseases to heel only to find that smoking, poor diets, and a lack of exercise are taking an increasing toll.

To reduce this toll through early detection, the Chinese Anti-Cancer Association in 2008 launched an effort to screen 530,000 women for breast cancer by the end of this year. The project includes training for at least 400 doctors. The health ministry is also funding a cervical cancer–screening program. The goal, Hao says, is to make screening a routine part of medical care. He would also like to see more basic cancer research. One mystery, Hao says, is that breast cancer is more common among women in their mid-40s in China than among same-aged women in developed countries; it's not clear why.

"The whole of society should be mobilized to control non-communicable diseases."

—YANG GONGHUAN, DEPUTY DIRECTOR OF THE CHINESE CENTER FOR DISEASE CONTROL AND PREVENTION

Off the scales

China's rapid economic ascent is embodied in richer diets and less physical activity. Yang Gonghuan and colleagues reported in their 2008 paper in *The Lancet* that people are eating less cereal grains and much more fat than they were 20 years ago. Salt consumption, presumed to increase the risk of hypertension, has risen to twice the level recommended by Chinese dietary guidelines. At the same time, city dwellers are driving more and bicycling less. As a result, urban Chinese are growing flabbier. According to Chinese body-mass indices, Yang Gonghuan reports that 22.8% of Chinese adults were overweight in 2002 and 7.1% were obese—double the rate reported in 1992.

Overeating begins in childhood. In Shanghai and Beijing, 29% of boys and 15% of girls aged 7 to 12 were overweight or obese in 2000, up from about 6% and 4% in 1985, C. M. Chen of the Chinese CDC reported online on 28 February 2008 in *Obesity Reviews*. Even infants are getting heavier. Lin Xu, a nutritionist at the Chinese Academy of Sciences' Institute for Nutritional Sciences in Shanghai, says there's been an increase in newborns weighing more than 4 kilograms, which is very heavy for Asian populations and can cause complications at birth and later in life. "Even medical professionals don't think of a big baby as a problem," Lin says. Some clinics are now trying to clue in caregivers and expectant mothers to the importance of a moderate weight gain during pregnancy, Lin says.

Poor diets, putting on pounds, and lack of physical activity are behind the rise in cerebro- and cardiovascular diseases and deaths, says Yang Gonghuan. These factors are also driving the diabetes increase. It's largely a silent epidemic: In the *NEJM* study, Yang Wenying says, 60% of Chinese with diabetes were unaware of their condition. Her group found that better educated people were more likely to know they have diabetes and take steps to control it. Particularly in rural areas, Yang says, "we need to educate people about [the benefits] of keeping a healthy lifestyle." They are planning a pilot program targeting 7000 adults with prediabetes, hoping to head off disease progression and complications that can include heart problems, ▶

Fat busters. Schools are turning to physical education to counter rising rates of childhood obesity.

CREDITS (TOP TO BOTTOM): (SOURCE) YANG GONGHUAN ET AL., THE LANCET 372, ISSUE 9650 (8 NOVEMBER 2008); NEWSCOM

limb amputations, and renal failure. And they are screening DNA samples collected from their 46,000 subjects to see if Chinese have a genetic susceptibility to diabetes.

The droves of undiagnosed diabetes cases point to a fundamental weakness in China's health care system. Clinics and hospitals "are not set up to identify people with the precursors to diabetes. They don't routinely test people, even people who might have a history of diabetes in the family," says Brian Oldenburg, a public health specialist who heads the Initiative for Global Health Improvement at Monash University in Melbourne, Australia. Oldenburg, who is advising Beijing health officials on how to reduce the diabetes burden, says it will be critical to identify people at risk and get them into programs to modify their behavior. The challenge, he says, is to "reorient a health system focused on child and maternal health and infectious diseases to help people manage a chronic disease like diabetes."

Improving disease prevention will take new regulations, awareness campaigns, and leadership by health care professionals, says Lincoln Chen. The China Medical Board has a program to urge doctors to stop smoking and adopt and enforce no-smoking rules in hospitals and clinics. Yang Gonghuan wants the food industry to cut back on salt as part of a broader effort to rein in hypertension And to battle diabetes, Chen Yan, who heads the Institute for Nutritional Sciences, says he and others are lobbying the government and industry to fortify milk products with vitamin D. Recent studies have found that more than 90% of middle-aged and older people in Beijing and Shanghai suffer vitamin D deficiency, which exacerbates diabetes and prediabetes.

The central government is tuning in to the shifting disease burden. In spring 2009, the State Council adopted sweeping health care reforms that aim primarily to broaden coverage and improve delivery. The plan also calls for hepatitis B vaccinations to stave off liver cancer and breast and cervical cancer screening. "It's a start," says Yang Gonghuan, who argues that greater emphasis should be placed on tobacco control and tackling stroke and heart disease.

China was caught off-guard by an "onslaught of chronic and noncommunicable diseases," says Lincoln Chen "I have no doubt that the Chinese will respond as recognition mounts and as health care costs mount, but how quickly and how effectively they can respond is not known," he says The key may be teaching a lesson that many Westerners are only beginning to fathom: The "good life," without moderation, can be bad for one's health. **–DENNIS NORMILE**

CREDIT: ZHANG WANXING

ARCHAEOLOGY

Unprecedented Excavation Brings Maritime Silk Road to Life

Raising the medieval *Nanhai 1* wreck was a technical tour de force; now archaeologists are preparing to take the vessel apart plank by plank

HAILING ISLAND, CHINA—In 1987, treasure hunters searching for a 16th century shipwreck off the coast of southern China stumbled instead upon relics from a much older merchant vessel. The serendipitous find "confirmed the existence of an ancient maritime trade route linking China and the West," says Zhang Wanxing, vice director of Guangdong Maritime Silk Road Museum here. In an unprecedented feat 20 years later, the 30-meter-long, 10-meter-wide ship, called *Nanhai 1*, or *South China Sea 1*, was scooped up along with a thick blanket of silt that entombs and preserves it, and hauled en masse to the museum. Now, at long last, archaeologists are about to embark on the next stage of *Nanhai 1*'s journey: a plank-by-plank excavation that will recover upward of 80,000 artifacts nestled inside.

A preliminary excavation last autumn lifted the veil on medieval Chinese shipbuilding, whetting appetites for more. The next phase will be "the first systematic and comprehensive study of a maritime silk route ship and its cargo," says archaeologist Bill Jeffery of James Cook University in Queensland, Australia. "Nothing like it has ever been done before anywhere in the world."

Chinese merchant vessels plied the Maritime Silk Road. from about the 2nd century B.C.E. to the 18th century C.E., starting out from ports along China's southeast coast and making for lands as far away as India and the Middle East. A handful of wrecks from the period had yielded precious few artifacts until *Nanhai 1*, which promises to shed light on everything from navigation and shipbuilding to porcelain making and metalwork, says Wei Jun, vice director of Guangdong Cultural Relics Bureau. And as *Science* went to press, salvage archaeologists were about to commence recovery of relics from another Silk Road era wreck, *Nan'ao 1*, off the coast of Guangdong.

Nanhai 1's serendipitous recovery began in the summer of 1987, when Guangzhou Salvage Bureau of the Chinese Ministry of Communications and Maritime Exploration and Recovery Ltd. were searching for the *Yhrhynsburg*, an East India Company vessel known to have sunk near the Chuanshan Archipelago in the South China Sea, off the coast of Guangdong Province. Scouring the seabed, the treasure hunters made an intriguing discovery: green porcelain bowls and other relics that were at least 800 years old. Chinese officials immediately halted the operation and called in archaeologists. The relics pegged the wreck to the Song Dynasty, which lasted from 960 C.E to 1279 C.E. Archaeologists were especially astonished by a 1.7-meter-long golden belt that was like

Westward bound. Now moored in mud in a museum, *Nanhai 1* (*left*) is one of two major wrecks from the Maritime Silk Road.

***Nanhai 1* treasures.** Porcelain (*left*) and a golden belt.

nothing they had seen before. "The ornamentation was totally different" from anything else made in China at the time, says Zhang Wanxing. "Everybody was shocked and excited," adds Cui Yong, vice director of the Underwater Archeology Research Center of the Guangdong Provincial Institute of Cultural Relics and Archaeology.

The first formal underwater excavation began in 1989. Zhang Wei, director of the National Underwater Team and vice director of the National Museum of China, found a wooden block—perhaps part of a mast—and a second diver found a fragment of porcelain. Those were the only two items recovered by divers until 2001, when an excavation sponsored by the Hong Kong China Underwater Archaeology Research and Exploration Association netted more than 6000 objects, including ceramics, coins, and metalwork. From 2002 to 2004, a $5.9 million program undertaken by the National Museum of China used radar soundings to map out *Nanhai 1* and confirmed the excellent condition it appeared to be in.

A huge decision confronted the experts: whether to excavate *Nanhai 1* where it lay or haul it ashore first. One other wreck had been raised intact successfully: the *Vasa*, a 17th century Swedish warship that was lifted from the bottom of Stockholm harbor in 1961 (*Science*, 12 September 2003, p. 1459). But *Vasa* was a special case: The harbor's frigid, less saline waters had shielded its hull from marine worms that devour wood. *Nanhai 1* was saved by silt that had quickly engulfed it.

On a visit to China in 2004, George Bass of the Institute of Nautical Archaeology (INA) in College Station, Texas, widely considered the father of marine archaeology, recommended that *Nanhai 1* be excavated like almost all other wrecks have been: by disassembling it on the seabed. Zhang Wei agreed, envisioning a 2-year-long in situ excavation. But in 2005 an expert panel organized by the National Heritage Board of China opted instead for a more ambitious plan proposed by the Guangdong government.

The $13 million salvage operation, using a 530-ton steel container specially designed for *Nanhai 1*, was "dangerous and difficult," says Zhang Wanxing. Engineers slid 36 steel beams, each weighing 5.3 tons, through 15 meters of mud—with an allowance for error of less than 10 centimeters in the murky water. They succeeded, and once *Nanhai 1* was cradled in its container, a floating crane that bobbed precariously on the swells raised it to the surface.

The success put Chinese underwater archaeology on the map—and left Bass, for one, "awed." "We carried out an excavation that no other country had dared to try," says Zhang Wanxing. Jeffrey, too, is impressed. "It is something you dream about: sealing the ship and all its cargo and fittings inside a large container, raising it, and bringing it ashore so you can excavate it in sheltered, cleaner, and warmer waters," he says.

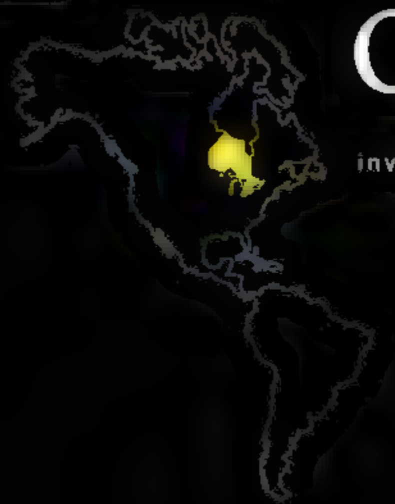
The groundbreaking operation spawned a new concern, however: how long *Nanhai 1* can hold up in its present environment. "Leaving it in water would be highly unusual, as this will eventually degrade the wood," says INA archaeologist Shelley Wachsmann. Although *Nanhai 1* is still submerged in seawater, says Zhang Wei, "it's uncertain how to maintain the chemical and physical environment ... and whether the boat can be protected." Simulations done at Sun Yat-sen University in Guangzhou have provided some guidance on ideal conditions for *Nanhai 1*. But "it is not so easy" to put theory into practice, says Zhang Wanxing.

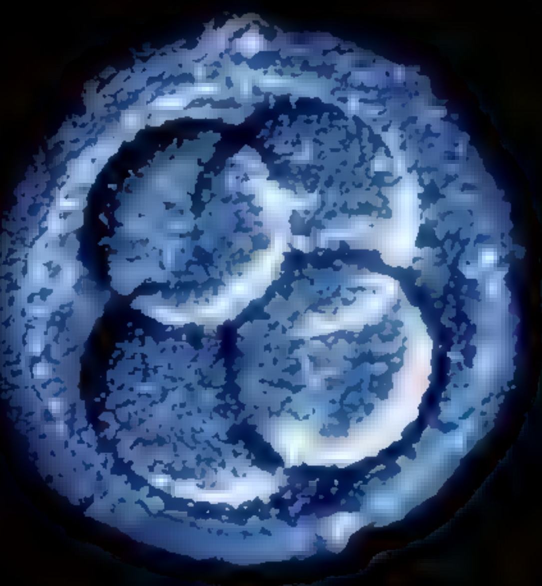
Zhang Wei and others also had nagging doubts about whether *Nanhai 1* survived the move to Hailing, about 75 kilometers from the salvage site. A preliminary analysis organized last summer by Guangdong provincial Institute of Cultural Relics and Archeology was reassuring: *Nanhai 1*, they found, is intact. "That set my mind at rest," says Zhang Wanxing. The team also excavated portions of the hull and recovered more than 200 artifacts, mostly porcelain. Protecting the ship's integrity is now the top priority.

Once archaeologists are satisfied *Nanhai 1* can withstand further scrutiny, they will begin a methodical disassembly. The excavation will be carried out in full view in the $22 million museum, which opened last December. "It's really a good opportunity for the public to learn about underwater archaeology," says Zhao Jiabin, director of the Underwater Archaeology Research Center of the National Museum of China. The museum already has loads of artifacts on display and in its storerooms that will help scholars fathom the maritime Silk Road, says Zhang Wanxing. And more secrets are waiting to be revealed. **–LI JIAO**

Li Jiao is a writer in Beijing.

CREDITS: (MAP SOURCE, SUI YI; INSET) COURTESY ZHANG; NATIONAL MUSEUM OF CHINA





LETTERS

edited by Jennifer Sills

Unconventional Journals: Research Ramifications

THE NEWS OF THE WEEK STORY "ELSEVIER TO EDITOR: CHANGE CONTROVERSIAL JOURNAL OR RESIGN" (M. Enserink, 12 March, p. 1316) reports on the withdrawal of a controversial HIV paper from *Medical Hypotheses*, a journal published by Elsevier. The paper in question claimed to refute the pivotal results of the National Heart, Lung, and Blood Institute Transfusion Safety Study, which revealed that 111 of 124 (89.5%) recipients of a single unit of HIV-infected blood became infected and that the rate of progression to AIDS within the first 38 months after infection was similar to that reported for homosexual men (*1*). Given such compelling data in support of HIV as the etiologic agent of AIDS, published in a prestigious medical journal, it was strange that Duesberg and Rasnick (*2*) put forth their hypothesis in 1998 that HIV does not cause AIDS. Propaganda exemplified by Duesberg's first and subsequent papers on the subject, and coupled with information freely disseminated through the Internet (e.g., http://en.wikipedia.org/wiki/AIDS_denialism), has indeed distracted from confronting AIDS in South Africa. Elsevier's due diligence in a responsible withdrawal of Duesberg's recent paper from *Medical Hypotheses* is commendable and will hopefully put an end to perpetuation of a dogma that is damaging to science and society. Only an effective HIV vaccine can ultimately end this drama.

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Readers' Poll

Unconventional Journals

The non–peer-reviewed journal *Medical Hypotheses* considers "radical, speculative and non-mainstream scientific ideas."* Recently, the journal has drawn fire** for publishing papers that some say are detrimental to health care efforts (see Letter by G. N. Vyas). Others feel that the journal is a "refreshing source of independent thinking" (see Letter by O. S. Amit). The future of *Medical Hypotheses* is now unclear. What do you think?

In general, do the benefits of a journal such as *Medical Hypotheses* outweigh the risks?

❒ Yes
❒ No
❒ Not sure

Vote online at www.sciencemag.org/extra/polls/20100423-1.dtl

*www.elsevier.com/wps/find/journaldescription.cws_home/623059/authorinstructions
M. Enserink, *Science* **327, 1316 (2010).

Polling results reflect the votes of those who chose to participate; they are not derived from a scientific random sample.

Unconventional Journals: Protect Nonconformists

I WAS DISMAYED TO LEARN THAT ELSEVIER intends to remove Bruce Charlton as editor-in-chief of the journal *Medical Hypotheses* and to convert the journal to peer-review format ("Elsevier to editor: Change controversial journal or resign," M. Enserink, 12 March, p. 1316). I find *Medical Hypotheses* to be a refreshing source of independent thinking in a sphere of scientific publishing that is becoming increasingly conformist, repetitive, and sometimes outright boring.

The current controversy around *Medical Hypotheses*—anger over papers claiming that HIV does not cause AIDS—highlights a major threat to the future of independent scientific thinking. The scientific community is undergoing continual division into exclusive clubs whose members are hostile to outsiders and their ideas. Nonconformists find it increasingly difficult to receive funding, secure tenure, and publish their hypotheses and results. This is particularly true in medical and biomedical research.

Underlying this trend is the unfortunate fact that increasing specialization has led many scientists to dedicate their entire careers to very narrow lines of research. These scientists may see their careers crumble should the theoretical framework underlying their research become unstable. Consequently, they have strong incentives to keep paradigm-shifting ideas away from the limelight. *Medical Hypotheses* was established to give an outlet to these potentially revolutionary ideas.

The hysteria surrounding the controversial HIV paper is particularly alarming, and some of the measures suggested, such as canceling *Medical Hypotheses* subscriptions and removing it from the MEDLINE database, are outright draconian. Those who claim to be scientists should use facts and reason, not censorship, to refute opposing views. This resort to censorship underscores the indispensable role of *Medical Hypotheses* as an outlet for new and challenging thoughts.

Forcing *Medical Hypotheses* to submit to peer reviews would turn it into yet another establishment journal, thus depriving it of its essence and uniqueness. It might as well be renamed *Mundane Hypotheses*.

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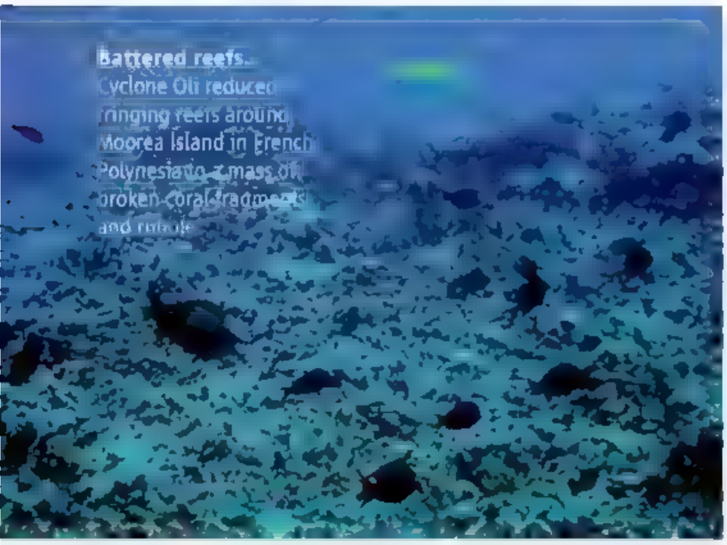
Tempestuous Times in the South Pacific Islands

IN RECENT WEEKS, A NUMBER OF CENTRAL South Pacific nations and territories have suffered a battering from an onslaught of intense cyclones occurring in quick succession. In early February, tropical cyclone (TC) Oli thrashed remote Tubuai in French Polynesia, tearing down buildings and pulverizing coral reefs (*1*). Just days afterward, TC Pat devastated biodiversity and coastal ecosystems on Aitutaki atoll in the Southern Cook Islands, on which the local tourism-based economy critically depends (*2*). TC Rene in mid-February triggered landslides in American Samoa before sweeping through the Kingdom of Tonga (*3*), and then mid-March saw TC Tomas pummel Fiji with waves up to 7 m (*4*) and wind gusts of 250 km/hour (*5*). The calamitous effects wrought by these four violent storms on built infrastructure and natural environments alike prompted national authorities to declare states of disaster.



Battered reefs. Cyclone Oli reduced fringing reefs around Moorea Island in French Polynesia to a mass of broken coral fragments and rubble.

Pacific Islanders should be admired for their resilience to natural hazards, which is underpinned by strong traditions of voluntarily assisting others facing hardship (*6*). Nonetheless, even with traditional kinship support and modern disaster response efforts, the demoralizing effect of broken homes, ruined subsistence crops, and other harsh impacts places a heavy burden on affected island populations (*7*).

Increasing frequencies of the most intense cyclones forced by climate change (*8*), coupled with potential future variation in cyclogenesis patterns, are likely only to worsen the vulnerability of island nations. Continuing hazard research must therefore remain a top priority to drive forward the implementation of culturally appropriate risk-reduction programs.

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CREDIT: S. ETIENNE

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Food Security: Translational Agriculture

IN THE PERSPECTIVE "RADICALLY RETHINKing agriculture for the 21st century" (12 February, special section on Food Security, p. 833) N. V. Fedoroff *et al.* rightfully propose a rethinking of the regulatory system to support public-sector development of genetically modified (GM) crops in the United States and as an international precedent. This strategy will only be effective if it is coupled with a comprehensive translational research paradigm for public agricultural research—analogous to the approach that the National Institutes of Health has been adopting since 2003 to better link basic research to patient needs.

In the past 20 years, private companies have only invested in the development of a few traits in a few major crops. As a result, specialty crops and traits with high environmental or social value but low economic value have been completely bypassed. Despite more than two decades of public research investment, only two GM crops developed in the public research sector have been approved for commercial release.

How can the public agricultural research sector implement a paradigm of translational research? First, researchers in agricultural biotechnology should anticipate the downstream development, deployment, and commercialization requirements from the start, rather than as an afterthought. They should address regulatory requirements and intellectual property access, and they should determine how to bring the project results to scale. Second, to achieve both basic research goals and successful translation, research teams should include members from multiple disciplines and maintain a high degree of connectivity and communication. Finally, translational research should be characterized by clear accountability focused on progress toward deliverables.

Philanthropic sponsors of agricultural development are now beginning to demand clearly articulated translational research strategies that encompass these components. If the public sector is going to contribute in tangible ways to Fedoroff *et al.*'s vision of the future of agriculture, the public research system needs to be tuned up for translation.

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Letters to the Editor

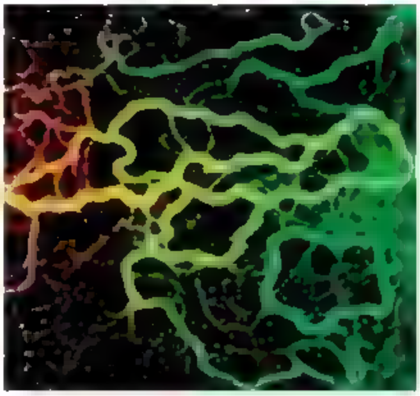
Letters (~300 words) discuss material published in *Science* in the previous 3 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

COMPLEX SYSTEMS

An Informative Itinerary

Iain D. Couzin

The "complexity barometer" is simple Look carefully into a fellow scientist's eyes and say the words "Santa Fe Institute" (SFI). The response is remarkably binary: a rolling of the eyes and an exhalation of air (a sort of desperation) or an immediate glint of excitement at the prospect of discussing the home of complexity and the cascade of ideas that have been forthcoming from the institute. Its own Web site has a section titled "The edge of respectability"—echoing the phrase "the edge of chaos," coined by SFI physicist Doyne Farmer—which openly describes this position within the scientific community. Many complex systems, and perhaps the institute itself, the metaphor suggests, should be poised at a "critical" point between disorder and order, a region suggested to maximize information processing. This is itself one of the most interesting, yet controversial, concepts to have emerged from complexity research. And here lies one of the central challenges to those working in this community, to provide concepts that are sufficiently rigorous and well defined to be more than just a metaphor, to be useful.



Simulated foraging. A complex network formed by ants responding to their chemical trails and to contact with one another.

Melanie Mitchell is well aware of this predicament as she takes us on a personal guided tour in *Complexity*. I emphasize personal because Mitchell (a computer scientist at Portland State University and SFI) uses her experience in evolutionary computation and artificial life to paint her picture of the history, and current state, of complexity research. Also, she writes in an unpretentious style with frequent entertaining and useful anecdotes that make one feel she is a trusted companion on the tour. Lastly, she focuses predominantly on computational aspects, with ecology, economics, and (perhaps surprisingly) neuroscience being notably less emphasized.

Almost immediately, Mitchell addresses the thorny issue of defining what is meant by a complex system: "a system in which large networks of components with no central control and simple rules of operation give rise to complex collective behavior, sophisticated information processing, and adaptation via learning or evolution." Like her, here I want to avoid the seemingly endless recursive discussions of what complexity is. However, given contemporary knowledge of biological organization (from neuronal circuits to flocking birds), it seems perhaps hasty to deemphasize the mutual presence of, and balance between, hierarchical and decentralized control and the role this can play in adaptive response.

Engagingly, Mitchell's tour offers the opportunity to touch on the history of many fundamental and transformative scientific discoveries, from those of information theory and quantum phenomena to that of dynamics. The book excels here; although the tour is fast paced, one doesn't feel that the guide is overly rushed. She captures the excitement of research and explains non-intuitive phenomena such as Maxwell's demon with clarity (and apparent effortlessness), making this an ideal guide for young scientists. Similarly, her summaries (although brisk) of entropy, information theory, and computation provide novice readers with a comprehensive overview.

Mitchell shows, however, that relating these concepts to real adaptive systems is problematic. As she highlights, pure information theory, although conceptually appealing, often cannot apply directly to real biological systems. Literal measures such as Shannon entropy can equate increasing complexity with increasing randomness. While algorithmic information content and modifications thereof (such as Gell-Mann and Lloyd's "effective complexity") are meaningful, it is clear that no one quantitative measure of complexity has yet emerged as generically useful in complex systems research.

One theme running through the tour is that we may learn much about adaptive behavior in general from understanding the principles of computation in man-made systems such as Turing machines and cellular automata. In such systems, simple local rules of interaction can result in sophisticated patterns of activity. Those, in certain cases, have been shown to be capable of "universal computation" (computing anything that is computable). Mitchell correctly cautions that both the necessary starting conditions and the required computational time could be limiting factors in the application of these ideas to real information processing as in the brain. But their remarkable properties, and the means of their discovery, make for fascinating reading.

The connection of this type of computation to insights about biology, however, is occasionally frustrated by an oversimplistic representation of natural processes For example, the author's imprecise description of evolutionary principles excludes important factors such as disease and predation pressures. Similarly, the description of ant colony behavior reads as a caricature, much as in decade-old complexity literature. Furthermore, I was surprised that Mitchell dismisses so readily "nonequilibrium, stability, bifurcation and symmetry breaking, and long-range order" as being "disparate concepts" that do little to explain complexity in nature. As highlighted in Philip Ball's recent series of books (*1*), those seem to be useful principles by which to understand biological self-organization, from how our heart beats to how ant colonies forage.

These issues aside, I thoroughly enjoyed Mitchell's tour of complexity. She proves an enthusiastic, sincere, and knowledgeable guide to ongoing debates in network theory, scaling, and artificial intelligence. As disciplinary boundaries fade and complexity science permeates the mainstream, she questions where we go from here. Throughout, she neither overemphasizes the progress made so far nor underestimates the important role that complexity research will have to play in addressing some of the most pressing scientific questions of our time. Thankfully, I think I'll be putting my complexity barometer to use for many years to come.

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ANTHROPOLOGY

What's Lost When Languages Are

Acrisio Pires

Partly due to a historical development marked by worldwide colonialism, urbanization, and globalization, in the course of this century humankind is likely to experience its most extreme cultural loss. As K. David Harrison notes in *When Languages Die*, "The last speakers of probably half of the world's languages are alive today." Their children or grandchildren are pressured (at times, by law) to speak only the dominant language of their community or country. Under one estimate, more than 50% of the 6900 or so languages identified nowadays are expected to become extinct in a matter of a few decades.

The precise criteria for what counts as a distinct language are controversial—especially those regarding closely related linguistic systems, which are often inaccurately referred to as dialects of the same language (*1*). The problem is complicated by the insufficiency of studies about the grammar (formal structure) of many of the world's endangered languages. In addition, from a cognitive standpoint any two groups of individuals whose languages are mutually intelligible may in fact have distinct mental grammars (thus, distinct languages, as established for instance on the basis of distinct parameters of grammatical variation in generative linguistics).

As a cognitive system, a language shows dynamic properties that cannot exist independently of its speakers. This is the sense in which the Anatolian languages and Dalmatian are extinct. Therefore, language preservation depends on the maintenance of the native-speaking human groups. Unfortunately, the most accelerated loss of distinct languages takes place where economic development is rapid, exacerbating the breakdown of minority communities that speak different languages. In this perspective, a language often begins to die long before the passing of the last speaker. New generations may start using it only for limited purposes, increasingly shifting to the community's dominant language. In this process, knowledge of the dying language erodes both at the individual level (language attrition or incomplete acquisition) and at the community level (language death).

Still speaking their native tongue. Antonio Condori and Illarion Ramos Condori, Kallawaya speakers, with David Harrison in the Bolivian Andes.

CREDIT: COURTESY LIVING TONGUES INSTITUTE FOR ENDANGERED LANGUAGES

When Languages Die
World's Languages and the Erosion Human Knowledge
by K. David Harrison
Oxford University Press

Just as an ecosystem becomes less rich by the extinction of a species, so too does a society with the extinction of a language. Presenting many case studies, Harrison (a linguist at Swarthmore College) argues that the extinction of a community's language entails major loss of knowledge of its cultural heritage (e.g., history, folklore, literature, and music) and of its understanding of the local flora, fauna, and ecosystem. Still, although these close ties do exist, the maintenance of a language and of other aspects of cultural heritage are not always mutually dependent. Cultural change can sometimes be the best guarantee that a group will be able to maintain its language and even survive. Major world languages (including English, French, Hindi-Urdu, and Spanish) achieved dominant status partly because of their speakers' ability to overcome, by means of cultural or technological change, the challenges and threats from their environment, including other peoples.

Linguistic diversity itself may be the worst loss at stake, because it may be the most promising and precise source of evidence for the range of variation allowed in the organization of the human cognitive system. For instance, Harrison discusses many strategies for manipulating quantities across languages, often endangered ones (*2*). Certain linguistic phenomena are only rarely encountered in the world's languages. Urarina, an Amazonian language spoken by fewer than 3000 people, possesses the exceptionally rare object-verb-subject word order. Click sounds are common only in the Khoisan languages spoken in southern Africa. The rapid loss of such diversity substantially hinders comparative investigation about the multiple ways in which a single cognitive domain can be organized. Linguists are well aware that their efforts alone cannot prevent this loss. Community involvement, especially with government support, has proven essential in slowing or even reversing language loss in different cases (e.g., Basque and Irish). Crucially, endangered languages must be acquired by new generations of speakers. Here the biological metaphor adopted by Harrison applies appropriately documentation of dead languages is akin to a fossil record, providing only partial clues about complex cognitive systems.

Nevertheless, our faculty of language naturally gives rise to innovation. As individuals acquire a language, they are bound to introduce changes into their grammars, thus creating new linguistic systems over time (*3*). This is a sense in which Latin and the unattested Proto-Indo-European did not die, but evolved into many new languages. Given such continuous innovation, one could ask why the impending disappearance of many languages should be so dire. Several factors make the losses irreparable: Current language diversity likely arose over tens of thousands of years. Despite the limitations of historical linguistic reconstruction (*4*), with sufficient data it can provide important clues about the path of development of human groups across the planet (*5*). Lastly, no amount of innovation over time will exactly restore current language diversity. As Harrison discusses, it was enabled mainly by the relative or complete isolation among human groups over centuries, circumstances that may never occur again. Rich in details yet surprisingly easy to read, *When Languages Die* shows what we are losing.

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10.1126/science.1163922

EDUCATION

Assessing Literacy Across a Changing World

New literacy skills affect educational and labor-market outcomes and can be compared from country to country.

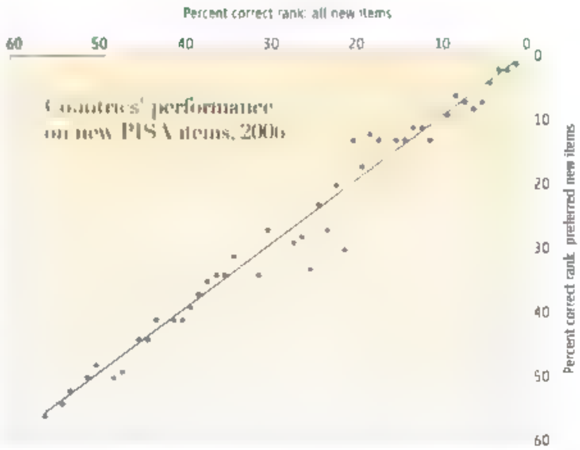
Andreas Schleicher

When public schooling began to expand access to education in the 19th century, literacy was mainly about learning to read, a set of technical skills that individuals would acquire once for a lifetime in order to process a fairly established body of coded knowledge For most, though not all, individuals in the industrialized world, those technical reading skills can now largely be taken for granted (*1*). But literacy requirements have shifted toward reading for learning the capacity to identify, understand, interpret, create, and communicate knowledge, using written materials associated with varying situations in changing contexts. These skills have now become an almost universal requirement for success in the industrialized world (*2*).

What Do We Need to Look For?

This shift in the concept of literacy is perhaps best illustrated with statistics on skill utilization in the labor force. It is no longer manual skills but routine cognitive skills that see the steepest decline in labor-market demand in advanced economies (*3*). Computers can replace humans for tasks involving processing of information through inductive or deductive rules, such as when issuing boarding passes at an airport. Routine cognitive skills are easier to outsource to foreign producers than other kinds of work: When a task can be reduced to rules (i.e., a standard operating procedure), the process needs to be explained only once, so communicating with foreign producers is much simpler than for non–rules-based tasks where each piece of work is a special case (*4*). The reproduction of a fixed body of knowledge, acquired with technical reading skills, is therefore no longer sufficient Individuals need the capacity to extrapolate from what they know, to use knowledge in new ways or situations, and to generate new knowledge.

Both the amounts and types of written materials have increased along with what individuals are expected to do with these materials. When the body of knowledge expanded slowly, it was sufficient to teach individuals how to locate information in an encyclopedia. Now, new digital forms of text make increased demands on readers and change the ways in which text is used (*5*). Readers must navigate through unstructured, conflicting information on the World Wide Web, making judgments as to the relevance and accuracy of what they read. Individuals often move through such material in their own ways when searching for information, creating their own "texts"; the total set of information each individual encounters is unique. Such skills required to use digital information are less well understood than traditional print skills but suggest that we will need to expand our definition of what it means to be literate.



Country rankings do not systematically increase or decrease if only countries' preferred PISA science items are considered. Diagonal line indicates slope of 1. Each point indicates a different country. Further details available in text and (*12*). Modified from figure 2 in (*12*).

How Do We Look Systematically?

How do education systems encourage transition to "new literacy skills"? Because the old saying that "what is tested is what gets taught" remains essentially true, many countries are monitoring student acquisition of literacy skills (*6*). But countries increasingly look to an internationally comparative context in which to interpret national performance and gauge progress. In a world where work that can be digitized and automated can be done by effective and competitive individuals or enterprises anywhere on the globe, relevant educational standards are no longer those of the city or state next door but those achieved by the best-performing education systems internationally.

International tests can illustrate what is possible, in terms of what the best-performing education systems show can be achieved, and they can foster better understanding of how different systems address similar problems. Such internationally comparative tests have been carried out since the 1960s (*7*, *8*). The latest generation was launched in 2000 with the Program for International Student Assessment (PISA) (*9*).

Comparative assessments of literacy skills need to fulfill different demands. Outcomes must be valid across cultural and linguistic boundaries. Tasks must be organized in ways that are authentic in different cultural and linguistic contexts, yet maintain the scientific integrity of the assessment such that characteristics that drive the difficulty of the tasks can be clearly defined and measured. Panels of international experts establish PISA literacy frameworks through three interrelated dimensions: (i) knowledge or structure of knowledge that students need to acquire; (ii) competencies that students need to apply; and (iii) contexts in which students would encounter problems (*10*).

For example, students at the highest PISA level of literacy (level 5) must be able to locate and use information that is difficult to find in unfamiliar texts, to show detailed understanding and infer which information is relevant to the task, to evaluate critically, to build hypotheses, to draw on specialized knowledge, and to accommodate concepts that may be contrary to expectations. By contrast, students at the baseline level of proficiency (level 2) (*11*) only need to be capable of basic reading tasks, such as locating straightforward information, making low-level inferences of various types, working out what a well-defined part of a

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text means, and using outside knowledge to understand it.

When developing assessment tasks that reflect the PISA frameworks, relying on the judgment of international experts alone does not suffice, not least because countries may conclude that unsatisfactory performance in an international test might just be the result of a culturally inadequate test. Important aspects of cross-cultural appropriateness and linguistic equivalence of tests can, however, be assessed empirically. For example, national authorities in each country determined to what extent each PISA task was culturally appropriate and reflected what students learned in school. Each country was scored on the complete international test, as well as on the subset of tasks that it considered most appropriate for inclusion in PISA. Although there was a tendency for countries to score slightly better on their "favorite" tasks than on the complete test, this was equally true for most countries, such that the rank order of countries remained largely unchanged (*12*, *13*) (see the graph on page 433).

Multiple-choice tasks are the most cost-effective way to assess knowledge and skills and have therefore dominated earlier international assessments. But they have limitations in assessing more complex literacy skills, particularly ones that require students not just to recall but to produce knowledge. Moreover, since the nature of and familiarity with assessment tasks vary across countries, reliance on any single item type can be a source of response bias. PISA developers have tried to address this through employing a broad range of assessment tasks, with about 40% of questions requiring students to construct their own open-ended responses. These allow for divergent responses and assessment of students' justification of viewpoints (*14*).

A challenge lies not just in ensuring that tasks are comparable across countries, but also that students respond in similar ways. For example, analyses suggest that student effort invested in PISA has been fairly stable across countries, countering the claim that systematic cultural differences in effort invalidate international comparisons (*15*).

How Do We Know That We Have Found It?

Ensuring that assessments are comparable across countries is critical. Another challenge relates to external validity, verifying that literacy assessments measure what they set out to measure and that those skills are predictive for future outcomes of individuals (*16*). In the case of PISA, the Canadian Youth in Transition Survey (YITS)—a longitudinal survey that investigates young people's major educational, training, and work transitions—provided a way to examine this empirically. In 2000 in Canada, 15-year-old students, 29,330 of them, participated both in YITS and PISA. Six years later, their educational outcomes were assessed and investigated for associations with PISA reading performance at age 15. Students who mastered baseline PISA reading level 2 were twice as likely to participate in postsecondary education at age 21 compared with those who performed at level 1 or below; those at level 5 were 20 times as likely compared with those at level 1 or below (*17*, *18*). Adult literacy surveys show that competencies such as those assessed by PISA are generally better predictors for earnings and employment status than the level of formal educational qualification that individuals had attained (*2*).

Future Challenges

Important aspects of the "new literacy" concept, especially elements of creating and communicating information, remain beyond the scope of large-scale comparative assessment. The 2009 PISA assessments mark the first time the reading of electronic texts has been assessed in an internationally comparative study; significant further efforts will be needed. As computers become more integrated with test delivery, there can be increased focus on more complex item types and the capturing and scoring of information that goes beyond simply determining whether a response is correct or incorrect. Improving predictive validity and cross-national comparability of tests continues to be challenging. The long-term future lies with multilayered assessment systems that extend from classrooms to schools to regional to national to international levels, that measure not just what students know but also how students progress, that are largely performance-based (*19*), that make students' thinking visible (*20*), and that allow for divergent thinking (*21*). Also, these assessments must generate data that teachers, administrators, and policy-makers can act upon.

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10. OECD, *The PISA 2009 Assessment Framework—Key Competencies in Reading, Mathematics and Science* (OECD, Paris, 2010).
11. The part of the performance distribution into which most respondents fall is cut into five equally sized levels. Some respondents fall below the lower bound of Level 1. Level 2 is considered "baseline," at which students have acquired basic building blocks for competency. Students below level 2 face disproportionately higher risk of poor school-work transitions and labor-market outcomes.
12. R. Adams, A. Berezner, M. Jakubowski, "Analysis of PISA 2006 Preferred Items Ranking Using the Percent-Correct Method" (OECD Education Working Paper 46, OECD, Paris, 2010); www.pisa.oecd.org/dataoecd/20/43/44919855.pdf
13. Rankings were remarkably consistent even when countries were ranked by average performance across every other country's subset of preferred items (*12*).
14. Open-ended assessment tasks raise other challenges, in particular, the need to ensure that they are rated consistently and fairly across schools and countries. For PISA, subsamples of assessment tasks need to be rated independently by up to four experts. An international coding review needs to be implemented to check on the consistency of application of response coding standards across all participating countries (*23*).
15. J. Butler, R. J. Adams, *J. Appl. Meas.* **8**, 279 (2007).
16. There is a tension between external validity and cross-national comparability that can be seen both in task formats (open-ended tasks aim at increasing external validity but are challenging in terms of achieving cross-cultural comparability) and context sensitivity (it is easier to assess recall of knowledge across countries than the application of knowledge, but the latter is critical for external validity). Trade-offs are made, for example, to protect against measuring in comparable ways things that may not be very important.
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18. A study in Denmark led to similar results. The percentage of youth who completed postcompulsory, general, or vocational upper-secondary education by 19 increased significantly with reading ability assessed at age 15 (*24*).
19. The actual performance of a student in solving a task is observed and measured, rather than merely the degree of correctness of their response.
20. Such tests support inferences about the manipulations, strategies, et cetera that students used. For example, PISA will try this in 2012 with an assessment of dynamic problem-solving, where everything students do will be recorded by the computer.
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NEUROSCIENCE

Escaping Attention

Some cognitive disorders can be overlooked.

Thomas Grüter and Claus-Christian Carbon

Cognitive neuroscience continues to unravel complex perceptional and cognitive processes of the human brain, in part by combining functional and anatomical aspects into network models. For example, the "dual-route" computational model of reading aloud (lexical and nonlexical routes from print to speech) has provided insights into how the process works and where its pathological variants, such as dyslexia (*1*), may originate. As well, the standard model for how we recognize other people's faces (*2*) has emerged from behavioral studies and sparse neuropsychological evidence available in the 1980s, and by more recent functional magnetic imaging studies of brain activity (*3*) and genetic analysis (*4*–*6*). Still, we are only beginning to understand the brain's cognitive function. One limitation is that static functional models of cognition remain a rough approximation of the brain's dynamic processing power. Another challenge is that some cognitive dysfunctions may not be so obvious.

Cognitive deficits in basic human skills are expected to draw attention. But, for example, dysfunction in a socially important cognitive task, such as recognizing people's faces, may not be apparent. The congenital type of prosopagnosia (*7*, *8*) or "face blindness"—the impaired ability to recognize faces on an individual level—was considered to be a rare condition. Surprisingly, though, it has recently been found to affect about 2.5% of the general population in Germany (*8*, *9*), despite the fact that it is generally not noticed in society. Other cognitive dysfunctions may have gone unnoticed as well, including voice agnosia (impaired ability to recognize people by their voices) or a hereditary type of color agnosia (impaired ability to recognize colors, even though the eyes distinguish them) (*10*, *11*). What might account for such invisibility?

It is difficult to define common features of conditions whose primary characteristic is that they have escaped attention. Therefore, a more informative question to ask may be, "What kinds of dysfunctions will most probably be found?" One consideration is that some cognitive requirements are culture-dependent. In a primitive, mostly illiterate society, a cognitive deficit would become apparent if, for instance, it prevents a person from becoming an expert archer. By contrast, dyslexia might never be noticed in these societies. Even in literate cultures, conditions differ: Dyslexic persons in China show a different pattern of brain activity in a reading task than do European dyslexics (*12*), and hence its detection might be culture-dependent. Moreover, skills can only be compared if they are practiced by a substantial number of people in a given cultural context. Otherwise, performance depends on the individuals' arbitrary state of training. As well, a sudden loss or decrease of a cognitive skill after a traumatic incident (such as a stroke or severe brain tissue damage) is not easily overlooked.

Yet cognitive dysfunctions that meet some of these conditions still may not be detected easily. For example, people may try to hide socially disabling or embarrassing impairments. Congenital prosopagnosia [being "face blind" from birth (*7*)] would be expected to lead to severe social restrictions, but, in fact, in most affected people it does not. Face recognition is only a subtask of the socially important task of person recognition. Impaired face recognition can, to a certain degree, be compensated for by other means, such as voice recognition or recognition of outer facial features such as hairstyle (*8*). In fact, most cognitive tasks are composed of subtasks that can be compensated for or substituted to some extent. A color-agnosic person may infer color by comparing the surface properties of a presented object with that of a known object (*10*). People with congenital agnosias have never known normal cognition, and therefore, they may have difficulty understanding or communicating the nature of their deficits. If a prosopagnosic, for example, complains to his doctor that he can't recognize people, the doctor may assume that the patient can't remember names, which is a very common memory problem.

A more general factor that may limit the discovery of cognitive deficits is the structure of cognitive tests. The human cognitive system adapts continuously. Thus, an assessment at a given point in time may not take into account flexibilities in reaction time, learning and processing speeds, or problem-solving techniques. For instance, a large meta-analysis of 107 samples—with a total of 134,436 participants given a cognitive ability test—revealed retest performance improvement of about one-half of the standard deviation from the first to the third test (*13*). The effect was larger when identical tests were used and

has also been observed for the quite complex Wechsler Adult Intelligence Scale (WAIS) test (*14*). Although the ability to adapt quickly to new challenges is a much sought-after skill in many professions, retest gains are treated as unwanted effects in many selection tests. Also, those skills for which a person is not specifically trained will only be developed to the socially accepted minimum. Thus, a standard cognitive test might miss a deficit in such a skill when cognitive dynamics are neglected.

Performances of many cognitive functions are distributed across a population in a normal (Gaussian) way, and thus "low performers" may be thought of as ordinary "tail-enders" in the distribution. There are also questions about the adequacy and scope of some contemporary cognition tests. For example, a

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type of hereditary color agnosia cannot be detected by the standard Ishihara color test for color blindness or the Farnsworth-Munsell 100-hue test for color matching (*10*). Tests for "general intelligence" (such as the Stanford-Binet and WAIS tests) do not reflect the function of a broad range of brain regions but mainly recruit a specific system in the frontal lobes (*15*).

Considering all these factors, some common cognitive dysfunctions may still await discovery. In Piaget's model of human cognitive development (genetic epistemology), children learn by assimilation, the fitting of the perception of a new event or object to existing schemes, and by accommodation, the adaptation of cognitive schemes to new percepts. With one or more dysfunctional cognitive skills, cognition may still reach a sufficient functional level, but the cognitive network will become stretched and bent in the process. Therefore, any congenital functional or anatomical differences, as in congenital prosopagnosia or protanopia (red-green color blindness), will cause the neural networks to develop and connect in specifically different ways and lead to typical behavioral changes.

These processes and the underlying functional and anatomical dynamics are an extremely promising field for further research. As well, cognitive tests could evolve in ways such as defining the scope of tests more precisely. The human cognitive system is praised for its enormous adaptability. To help affected persons and to acquire a more comprehensive understanding of the brain, greater attention needs to be directed toward the structures, dynamics, and limits of these adaptive processes.

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MOLECULAR BIOLOGY

Syntheses That Stay Together

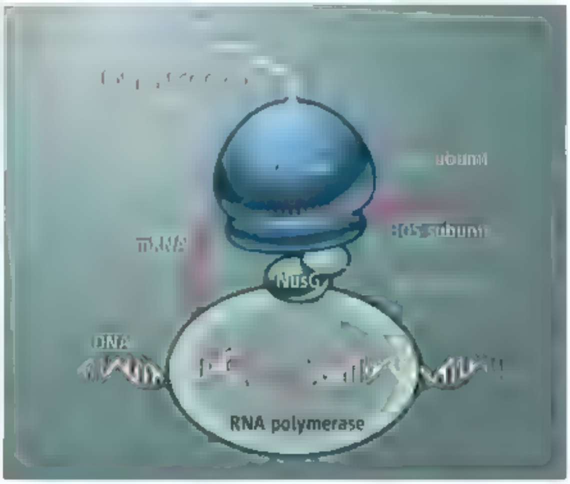
The rate of mRNA translation determines the rate of mRNA synthesis in bacteria through direct coupling of the respective molecular machinery.

Jeffrey W. Roberts

An old principle of macromolecular biosynthesis in bacteria is that the speed of protein synthesis (translation) matches that of messenger RNA (mRNA) synthesis (transcription), but how this integration occurs has not been clearly defined. An obvious conjecture is that ribosomes move along the emerging mRNA at whatever speed RNA polymerase goes so that translation and transcription remain coordinated, as it is known to do when conditions change (*1*). However, on page 504 (*2*) and 501 (*3*) of this issue, Proshkin *et al.* and Burmann *et al.*, respectively, suggest the opposite: Efficient binding and progression of ribosomes along mRNA increase the speed of RNA polymerase, whereas the absence of ribosomes allows the polymerase to slow and wait for ribosomes to catch up.

Proshkin *et al.* measured the rate of RNA polymerase progression along DNA in bacteria when translation was slowed in any of three ways: treatment with an antibiotic, expression of a mutated ribosomal protein, and an increase in the abundance of rare codons in the transcribed DNA. In each case, transcription slowed correspondingly. Furthermore, a ribosomal mutation that increased the rate of translation accelerated transcription.

What connection between RNA polymerase and ribosome underlies this unexpected effect? Proshkin *et al.* suggest that it depends on the polymerase's ability to "backtrack," in which it momentarily stops elongating mRNA and spools backward instead (*4*, *5*). Consequently, the newly synthesized mRNA end is extruded from the "secondary" channel of RNA polymerase and the upstream segment of mRNA is drawn back into the usual exit pore of the enzyme. RNA polymerase moves relatively freely between these isomeric states, although backtracking is favored when the mRNA-DNA hybrid is stronger in the backtracked position than in the forward position. Backtracking also is the response of polymerase to a physical barrier in its path, such as a DNA binding protein, even in the absence of an energetically favorable hybrid. A reasonable proposition is that temporary barriers in the chromosome make backtracking frequent enough to slow the overall rate of transcription. But backtracking is inhibited if another molecule binds to upstream mRNA and prevents its retraction into the enzyme (*6*). Along these lines, Proshkin *et al.* propose that a ribosome closely following RNA polymerase restrains the emerging mRNA. This would inhibit backtracking and favor net forward movement of the polymerase.



Coupled syntheses. A model for the coupling of translation and transcription in bacteria is shown. The first ribosome translating a mRNA associates with RNA polymerase through the NusE-NusG-polymerase interaction. This prevents retraction of the emerging mRNA into RNA polymerase, and thus inhibits backtracking-associated pauses that slow RNA polymerase in the absence of the ribosome.

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How does this mechanism relate to the fundamental regulatory step in which gene expression varies with the rate of ribosome access to its binding site at the beginning of the mRNA (*7*)?

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A strong binding site would allow a ribosome to load immediately onto the mRNA and prevent the advancing RNA polymerase from backtracking. At a weaker binding site, where the ribosome may not engage the mRNA immediately, the polymerase would slow through backtracking until a ribosome advances enough to cover the emerging mRNA, preventing backtracking. This ribosome then could accompany RNA polymerase to the end of the gene.

This model also explains how operons that are weakly translated—and thus have potentially extensive regions of naked mRNA coexist with a process, mediated by Rho termination factor, which detects untranslated mRNA and terminates transcription. Rho binds 70 to 80 nucleotides of naked mRNA emerging from RNA polymerase, so that infrequent ribosome attachment to mRNA might be expected to provide a target for Rho at high efficiency. However, if RNA polymerase slows to let the first ribosome catch up (a train of ribosomes follows the polymerase in step, forming a "polysome" on the mRNA), the polymerase will be protected from termination, even if there are few ribosomes bound to the mRNA. Rho acts at the (untranslated) ends of operons (*8*), and in addition is the agent of "polarity," the process that aborts transcription when translation stops at a nonsense codon in a gene (*9–11*). Because the ribosome that accompanies RNA polymerase (and all following ribosomes) would be removed as soon as the nonsense codon is encountered, emerging mRNA could quickly accumulate to the required length and promote Rho activity.

Further evidence for a direct connection between the ribosome and RNA polymerase is provided by Burmann *et al.*, who show through nuclear magnetic resonance (NMR) analysis direct binding between NusE, a ribosomal protein, and NusG, an RNA polymerase–binding protein (*12*)—an interaction also suggested by earlier genetic experiments (*13*) (see the figure). Because the NusG binding surface of NusE is exposed on the outside of the ribosomal 30*S* subunit, the leading ribosome could be tethered to RNA polymerase through NusE-NusG interaction, facilitating the ribosome's access to the emerging transcript and strengthening the inhibition of backtracking. NusG also binds to the Rho termination factor (*14*) and stimulates Rho function. Because Rho and NusG compete for binding to NusE, stimulation of Rho by NusG would be available only in the absence of a ribosome.

What happens to RNA that is not translated, such as ribosomal RNA (rRNA)? In *Escherichia coli* rRNA synthesis, RNA polymerase is modified by an antitermination complex that incorporates the transcription factors NusA, NusB, NusG, and NusE (*15*), this is similar to the well-characterized bacteriophage λ gene *N* antitermination complex (*16*, *17*). The antitermination complex of rRNA operons likely prevents termination of rRNA transcription by Rho. In addition, antitermination factors such as bacteriophage λ N and Q proteins and *E. coli* RfaH protein inhibit pausing and accelerate RNA polymerase (*18*, *19*); if it acts similarly, the rRNA operon antitermination complex may take the role of the leading ribosome in accelerating transcription.

There is also an alternate model to consider for the mechanism by which a ribosome accelerates transcription. The leading ribosome could act by the same pathway as the antitermination factors, which are thought to mediate changes in the active center of the polymerase that inhibit pausing, rather than acting simply to block mRNA movements associated with backtracking. These molecular details of the interconnection between translation and transcription are a fertile subject for future research.

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10 1126/science 1189971

CLIMATE CHANGE

Toward Understanding and Predicting Monsoon Patterns

Eugene R. Wahl[1] and Carrie Morrill[1,2]

A comprehensive atlas of past monsoon patterns will help scientists understand the causes of monsoon variability.

Much of the world's population lives in monsoon Asia and depends on monsoon rainfall for water and agricultural fertility. The monsoon also affects climate in other parts of the world (*1*). It results from an interplay between the ocean, atmosphere, and land surface (see the figure). Many factors thus affect its strength, including sea surface temperatures (SSTs) in the Indian and Pacific Oceans; variations in solar output; land snow cover and soil moisture over the Asian continent; and the position and strength of prevailing winds (*1*). The links between these factors and the monsoon appear to wax and wane over time, and the observational record is too short to explain this longer-term variability (*2*). This lack of information makes it difficult to forecast and plan for anomalous monsoon activity, and to predict how the Asian monsoon may be affected by global climate change. This situation is now changing: On page 486 of this issue, Cook *et al.* (*3*) report a Monsoon Asia Drought Atlas (MADA) that contains reconstructions of summer dryness and wetness for the region since 1300 C.E., based on tree-ring data.

The MADA offers a more comprehensive perspective on complex regional moisture patterns than that available previously from point source reconstructions (*4*). The new reconstructions cover three key climatic subperiods in the last millennium: the latter part of the Medieval Climatic Anomaly (*5*), the Little Ice Age, and the period of anthropogenic climate forcing. The length of the MADA record opens new possibili-

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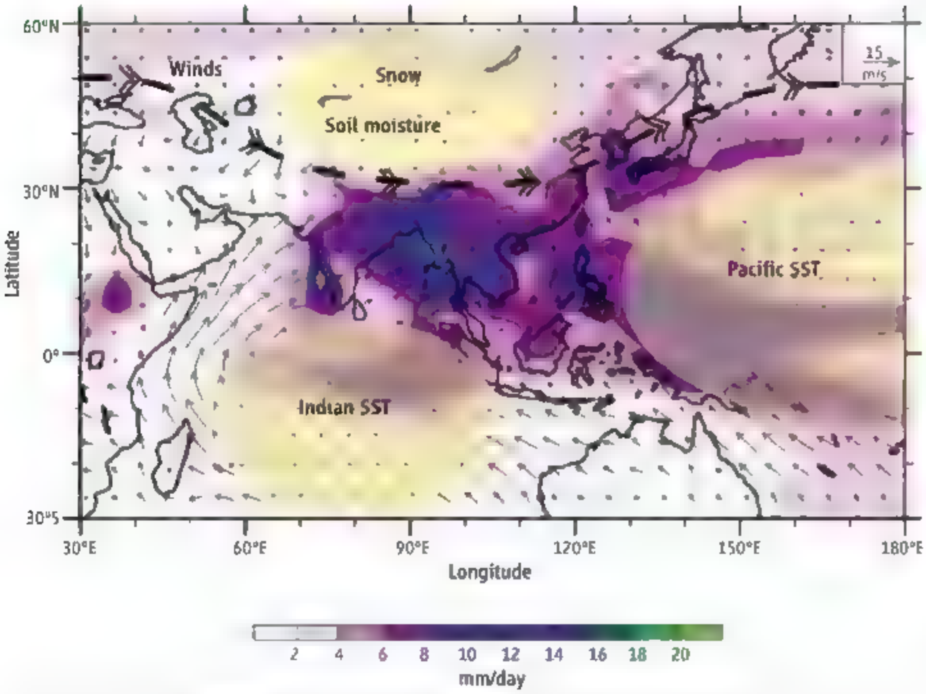

Complex interplay. Precipitation and surface wind maps over Asia during summer (June to August) show the average spatial patterns of monsoon circulation and moisture. Yellow areas and schematic of westerly winds indicate some factors that influence monsoon variability. Precipitation data are from the Global Precipitation Climatology Project v. 2.1 (http://precip.gsfc.nasa.gov), and wind data are from the NCEP/NCAR Reanalysis (www.cpc.ncep.noaa.gov/products/wesley/reanalysis.html). Both are averaged over the period from 1979 to 2009. All data were obtained from the National Oceanic and Atmospheric Administration (NOAA).

ties for understanding the global drivers of monsoon Asia's hydrologic dynamics, particularly in conjunction with the North American Drought Atlas (NADA) (*6*) and information about Pacific Ocean variability (*5*).

Cook *et al.* make good first steps in this direction. They show how both Asian and North American megadrought patterns in the late 19th and early 20th centuries are linked to Pacific SST patterns of the El Niño-Southern Oscillation (ENSO). Their methodology also makes it possible to identify rigorous mathematical subcomponents from the MADA data; this is crucial for showing that different types of Pacific SST patterns, including ENSO and the Pacific Decadal Oscillation (PDO), are associated with different drought patterns. The combined spatial patterns in the MADA and NADA can be used in climate model studies to test hypotheses about the effects of various SST patterns on monsoon precipitation.

Results from the MADA also confirm that drought and wetness in the monsoon region are spatially heterogeneous (see the figure), even though the region is under the influence of one large-scale circulation pattern commonly referred to as the monsoon. This fact is particularly important for predicting hydrological changes in the region. Reduced sulfate aerosol concentrations and increased greenhouse gas concentrations are predicted to intensify the monsoon in the long term (*7*), but it is likely that rainfall will continue to be spatially heterogeneous. It is, thus, essential that the causes of recent shorter-term trends pointed out by Cook *et al.* (such as increased moisture in Tibet and drier conditions in south and Southeast Asia) are identified. Are these trends part of a response to anthropogenic climate change, or are they part of inherent monsoon spatial variability?

A particular challenge for assembling the MADA has been the relative scarcity of long tree-ring records in this part of the world. This scarcity, together with gaps in observational data, may contribute to the fact that the reconstructions perform no better than long-term climate averages in matching measured moisture variations over significant portions of the MADA region during an independent test period (1920 to 1950). (A reconstruction that offers a better match than simply substituting the average during a test period is considered to have "skill.") Developing more tree-ring records is key for continued improvement of the MADA, similar to the ongoing development of the NADA (*6*).

Cook *et al.* performed two further tests of the MADA reconstructions. The results suggest the reconstructions are better than the above test indicates. The first additional test is particularly relevant to India and Pakistan and makes use of the very long observational record in these areas. It covers the period from 1870 to 1919 and shows continuous skill across the Indo-Pakistani subregion.

The second additional test is based on the patterns reconstructed in the MADA for four historically documented megadroughts, going back to 1638. The results show that the reconstructions capture hydrological patterns far back in time. For example, for the "Great Drought" of the late 19th century, the MADA detects not only known heterogeneous patterns of dryness, but also simultaneous extreme wetness along the southeastern coast of China (*8*). This coastal area does not show skill in the 1920-to-1950 test. The identification of drought pattern subcomponents, whose relative strengths over time correlate strongly with well-known Pacific SST patterns, also indicates that the reconstructions capture spatial drought information with good fidelity.

The MADA is a crucial step forward for paleoclimate studies in a region that is of great social and climatological interest, but where the development of tree-ring archives faces immense challenges and instrumental data coverage is limited. Tree-ring scientists continue to expand spatial coverage by discovering new sources of relict wood, rare species that faithfully record climate, and new geochemical indicators of climate variability within tree tissue. Making sense of the dynamic processes underlying the large amount of spatial and temporal detail in the MADA will be a challenge for climate modelers, but is a key goal on the road to improved predictions of monsoon precipitation.

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IMMUNOLOGY

Salmonella Susceptibility

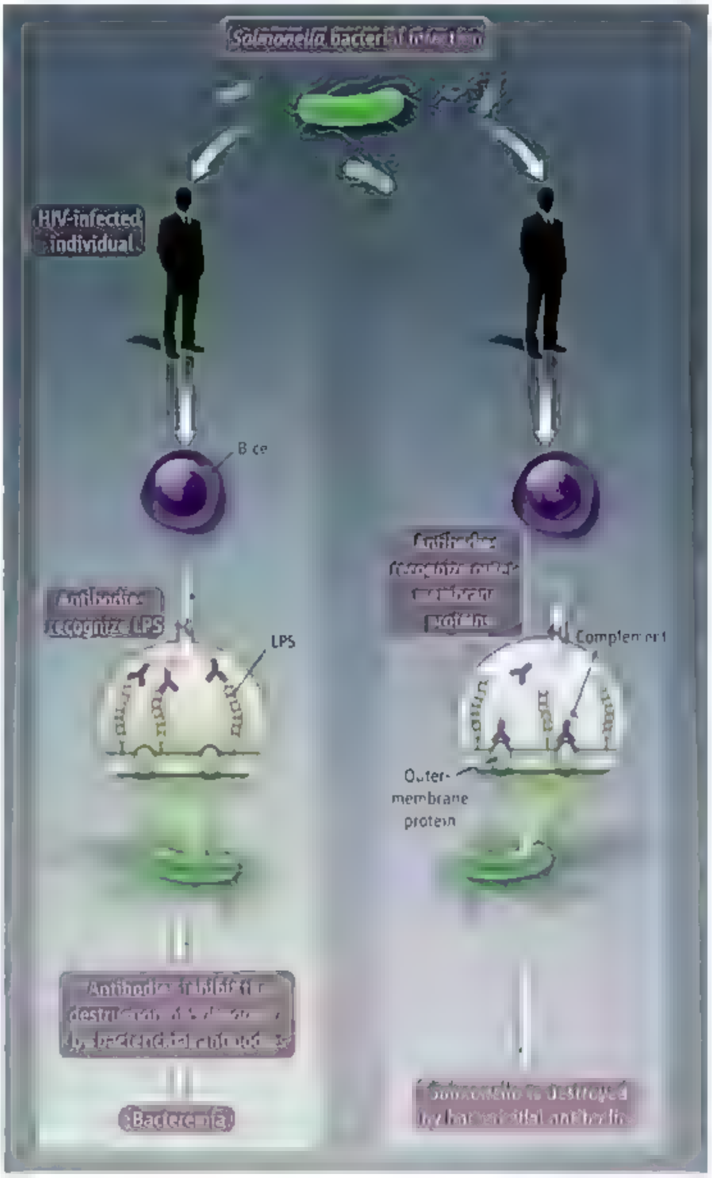
HIV-infected individuals produce antibodies to *Salmonella* that block the effects of protective antibodies

Susan Moir and Anthony S. Fauci

Nontyphoidal *Salmonella* (NTS) are a group of enteric bacteria that cause self-limiting gastroenteritis in healthy individuals but can lead to life-threatening bacteremia in those with weakened immune systems. Before the introduction of highly effective antiretroviral therapy in 1995–1996, NTS bacteremia was a common opportunistic pathogen associated with HIV infection (*1*). Today, in countries with limited availability of antiretroviral therapy, NTS remains an important cause of morbidity and mortality in HIV-infected individuals (*2*). On page 508 of this issue, MacLennan *et al.* identify an immune response that allows NTS to thrive in individuals infected with HIV, thus causing the normal immune reaction to NTS infection to be defective (*3*). This may have important implications for the development of a vaccine against NTS.

Until recently, immunity against NTS infection was thought to be primarily cell-mediated (*4*), consistent with increased susceptibility to this infection in individuals with T cell impairment. However, a prominent role for antibodies in protection against NTS bacteremia in African children (*5*) suggested that a humoral immune response may also be involved. Now, MacLennan *et al.* report a high concentration of antibodies against NTS in the serum of HIV-infected individuals that prevent the destruction of *Salmonella*.

If untreated, HIV infection usually leads to persistent HIV viremia, progressive depletion of T cells (CD4$^+$ subtype), and immune deficiencies. Paradoxically, HIV disease is also associated with excessive immune system activation. B cells of HIV-viremic individuals are characterized by an excessive polyclonal response—the production of different antibodies by many different B cells against many different antigens (*6*). Yet, antibody responses against various pathogens and immunogens are defective in HIV-infected individuals, in part because of deficient help from CD4$^+$ T cells, but also likely as a result of intrinsic B cell defects (*7*). Although MacLennan *et al.* expected to find a deficiency in the ability of HIV-infected individuals to generate NTS-specific antibodies, they found just the opposite: Defective killing of NTS was associated with increased concentrations of antibodies directed against NTS. After excluding a defect in the complement system, which is required for antibody-mediated killing of NTS (*5*), the authors postulated that inhibitory antibodies in the serum of HIV-infected individuals could be responsible.



Antibody block. In HIV-infected individuals, LPS-specific antibodies may divert complement or prevent bactericidal antibodies from binding to the outer membrane of nontyphoidal *Salmonella*.

Indeed, the sera of HIV-infected individuals proved to contain antibodies against NTS that inhibited the killing potential of sera from individuals not infected with HIV. MacLennan *et al.* found that the destruction of NTS is mediated by bactericidal antibodies directed against outer-membrane proteins (porins) of NTS, but antibodies directed against the lipopolysaccharide (LPS) that coats NTS prevented this effect (see the figure). Moreover, the bactericidal antibodies were detected in the sera of healthy individuals (and even in sera of HIV-infected individuals) and could restore NTS killing in serum previously shown to be deficient (*5*), as well as reverse the impaired NTS killing in sera of HIV-infected individuals. By testing variants of *Salmonella* and LPS, and also mouse bactericidal antibodies directed against the outer membrane of NTS, MacLennan *et al.* determined that the distal portions of LPS are targeted by the inhibitory antibodies, but how they prevent the effects of bactericidal antibodies is not clear. Inhibitory antibodies could block bactericidal antibodies from binding to their targets on the outer membrane and/or direct complement away from the bacterial membrane.

Why are these inhibitory antibodies specifically pro-

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duced in HIV-infected individuals, and why is NTS bacteremia only observed in patients with advanced HIV disease? The excess of antibodies to LPS in the serum of HIV-infected individuals was only weakly associated with hypergammaglobulinemia (increased antibodies in the blood), suggesting that polyclonal activation was not driving the expansion of LPS-specific antibodies. One explanation may relate to elevated amounts of LPS in the plasma of HIV-infected individuals. This is thought to result from HIV-induced disruption of the gastrointestinal mucosa and leakage or translocation of LPS from the gut into the circulation. (*8*). MacLennan *et al*. did not find a correlation between the concentrations of plasma LPS and LPS-specific antibodies, whereas there was a good correlation between the latter and impaired NTS killing (*3*). However, LPS might be associated with LPS-specific antibodies in complexes that are cleared from the circulation too rapidly for detection.

The presence of LPS-specific antibodies is likely to be only one of many defects responsible for NTS bacteremia in advanced HIV disease NTS bacteremia in immunocompromised individuals, including HIV-infected individuals, has been associated with defects in cell-mediated immunity, including cytokine deficiencies (*4*). In this regard, interleukin-17 deficiency induced by simian immunodeficiency virus infection was associated with NTS bacteremia, and a similar scenario was proposed for HIV infection (*9*).

The results of MacLennan *et al*. may have practical implications for vaccine development. Their findings suggest that bacterial outer-membrane proteins of NTS, as opposed to LPS, should be the preferred vaccine target because LPS could potentially elicit inhibitory rather than the desired bactericidal antibodies.

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10 1126/science.1189088

APPLIED PHYSICS

The Case for Plasmonics

Light-induced surface excitations may offer a route to faster, smaller, and more efficient electronics as well as new technology opportunities.

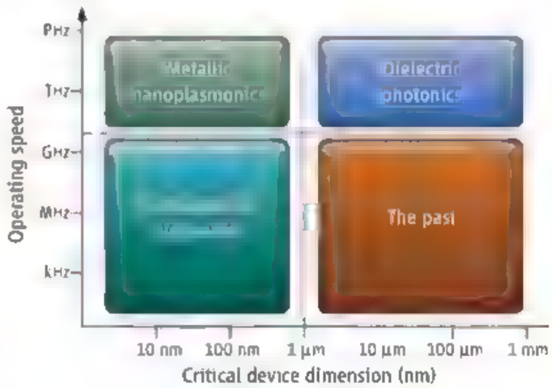
Mark L. Brongersma,[1] and Vladimir M. Shalaev[2]

Just over a decade ago, the term "plasmonics" was coined for a promising new device technology that aims to exploit the unique optical properties of metallic nanostructures to enable routing and active manipulation of light at the nanoscale (*1*). At the same time, it was already well established that tiny metallic particles have a number of valuable optical properties that are derived from their ability to support collective light-induced electronic excitations, known as surface plasmons. Most notably, nanostructured metals dramatically alter the way light scatters from molecules, and this later led to the development of an important optical spectroscopy technique called surface-enhanced Raman spectroscopy (*2–4*).

The plasmonics field exploded when it was demonstrated that metallic nanowires enable much smaller optical circuitry than dielectric (e.g., glass) waveguides (*5*), metal films with nanoscale holes can show extraordinarily high optical transmission (*6*), and a simple thin film of metal can serve as an optical lens (*7*). Plasmonic elements are also important as popular components of metamaterials—artificial optical materials with rationally designed geometries and arrangements of nanoscale building blocks. The burgeoning field of transformation optics elegantly describes how such materials can facilitate an unprecedented control over light by "engineering optical space" with local control of a metamaterial's response (*8*). As these novel phenomena captured the imagination of a broad audience, some of the severe limitations of metals were being recognized. The most important challenge is that metals exhibit substantial resistive heating losses when they interact with light. We have an opportunity to look back, evaluate the progress in the field, and look at promising future directions.

Plasmonics has enabled both exciting, new fundamental science and some real-life applications. The most important advances rely heavily on one key property of engineered metallic structures, that they exhibit an unparalleled ability to concentrate light. Even a simple spherical metallic nanoparticle can serve as a tiny antenna capable of capturing and concentrating light waves. By squeezing light into nanoscale volumes, plasmonic elements allow for fundamental studies of light-matter interactions at length scales that were otherwise inaccessible.

A diverse set of plasmonics applications has emerged in the past 10 years. Early applications included the development of high-performance near-field optical microscopy and biosensing methods. More recently, many new technologies have emerged in which the use of plasmonics seems promising, including thermally assisted magnetic



Of size and speed. The different domains in terms of operating speed and device sizes rely on the unique material properties of semiconductors (electronics), insulators (photonics), and metals (plasmonics). The dashed lines indicate physical limitations of different technologies; semiconductor electronics is limited in speed by heat generation and interconnect delay time issues to about 10 GHz. Dielectric photonics is limited in size by the fundamental laws of diffraction. Plasmonics can serve as a bridge between photonics and nanoelectronics.

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recording (*9*), thermal cancer treatment (*10*), catalysis and nanostructure growth (*11*), and computer chips (*12*, *13*). Interestingly, the first three applications in this list capitalize on light-induced heating, which was originally considered as a weakness of plasmonics. After the discovery that long-distance information transport on chips with plasmonic waveguides would suffer too strongly from heating effects (*14*), it now has been established that modulators (*12*) and detectors (*13*) can be realized that meet the stringent power, speed, and materials requirements necessary to incorporate plasmonics into conventional electronics technology. Plasmonic sources capable of efficiently coupling quantum emitters to a single, well-defined optical mode may first find applications in the field of quantum plasmonics and later in power-efficient chip-scale sources (*15*, *16*). In this respect, the recent prediction (*17*) and realization (*18*–*20*) of coherent nanometallic light sources constitutes an extremely important development. Looking even further down the line, the recent prediction that a surface plasmon laser may operate as an ultrafast amplifier is certainly stimulating. Could one build ultrafast logic circuits with devices that perform a similar function as the ubiquitous transistor but are orders of magnitude faster (*21*)?

As the complexity of plasmonic systems increases, the development of simple design rules for components is absolutely essential. The power of good design rules lies in their ability to hide much of the complexity within an individual device. Instead, the aim is to capture the essence of the device function and focus on its interactions with other devices. Such simplifications then enable the construction of system-level theories and simulators that can predict the behavior of larger circuits. Engheta recently developed an elegant theoretical framework that treats nanostructured optical or "metactronic" circuits much akin to conventional electronic circuitry (*22*)—insulators are modeled as capacitors, metals as inductors, and energy dissipation (heating) can be accounted for by introducing resistors. The desired response of an optical circuit can now be realized through the optimization of a little electronic circuit.

It has become clear what role plasmonics can play in future device technologies and how it can complement electronics and conventional photonics (see the figure). Each of these device technologies can perform unique functions that play to the strength of the key materials. The electrical properties of semiconductors enable the realization of truly nanoscale elements for computation and information storage. The high transparency of dielectrics facilitates information transport over long distances and at incredible data rates. Unfortunately, semiconductor electronics is limited in speed by interconnect delay-time issues, and dielectric photonics is limited in size by the fundamental laws of diffraction. Plasmonics offers the opportunity to combine the size of nanoelectronics and the speed of dielectric photonics, enabling devices that might naturally interface with similar-speed photonic devices and with similar-size electronic components, thus enhancing the synergy between these technologies. The semiconductor and photonics industries have continued to develop rapidly, and it will be exciting to see what the next decade will bring for plasmonics.

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PHYSICS

Sign Flips and Spin Fluctuations in Iron High-T_c Superconductors

The symmetry of electron-pairing interactions in iron-based superconductors suggests a shared spin-mediated pairing mechanism with the cuprate family.

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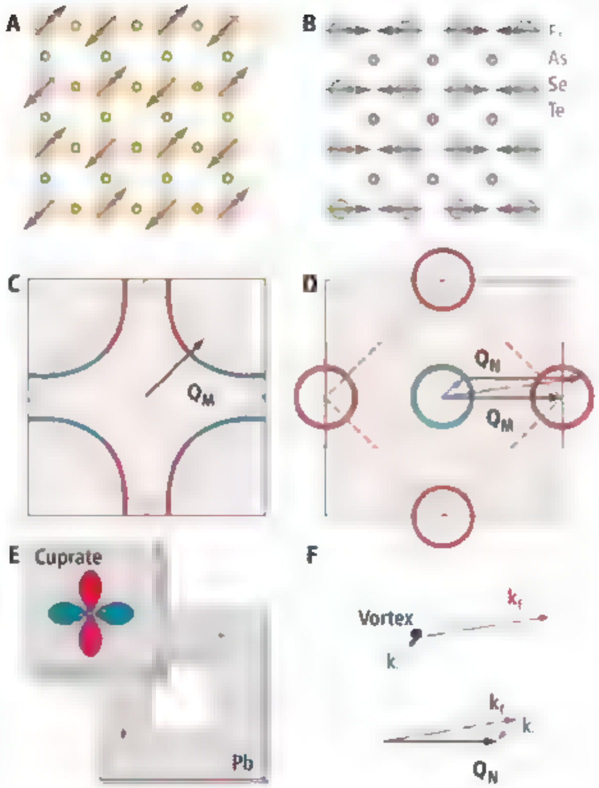
In superconductors, the key process that allows current to travel without resistance is the formation of electron pairs that move as a single quantum state. The mechanism of pairing in the high-temperature (high-T_c) cuprate superconductors is still elusive, so the recent discovery of iron-based superconductors (*1*) sparked the hope that comparison with the cuprates would lead to a better understanding of pairing in both materials. On page 474 of this issue, Hanaguri *et al.* (*2*) report the experimental determination of the pairing symmetry in $FeSe_xTe_{1-x}$. Combined with the recent observation of a spin fluctuation resonance in this material (*3*) akin to that seen in the cuprates (*4*), a compelling hypothesis emerges that these high-T_c superconductors share a common pairing mechanism.

Pairing in both conventional and high-T_c superconductors must overcome the large repulsive force between two like charges. In conventional superconductors, pairing arises from a normal metallic state, where electrons are numerous and move freely to screen any local inhomogeneity. One electron plus all of the screening electrons act like a single "quasiparticle." Despite the strong repulsion that should arise between any two isolated electrons, even a small attractive interaction such as a phonon—a wake of displaced ions—causes the pairing of quasiparticles. In conventional superconductors, phonon-mediated pairing is typically isotropic, with spherical or "*s*-wave" symmetry.

In high-T_c cuprates, the story is more complicated because their "normal" state has too few charge carriers to screen effectively. Electrons interact quite strongly, allowing

new pairing possibilities. Passionate voices have argued for several candidates, including phonons, exotic charge excitations, or a spin-mediated repulsive potential. This latter mechanism can pair two quasiparticles only if their wave functions have opposite sign (*5*). To decide between competing models, experiments must measure the symmetry of the order parameter: the dependence of both the amplitude and quantum-mechanical phase of the pairing potential on quasiparticle momenta.

In the cuprates, it took almost a decade to establish that the pairing symmetry is "*d*-wave" (*6*). Angle-resolved photoemission spectroscopy (ARPES) revealed four directions of quasiparticle momentum in which the pairing amplitude is zero; these are called nodes in the order parameter (see the figure, panels A and C). Quantum tunneling experiments in a corner junction geometry established that the phase changes sign between the four nonzero lobes of the order parameter (see the figure, panel E).



Spin fluctuations and symmetry. Common features can be found in the spin fluctuations and pairing symmetry in cuprate and iron-based superconductors **(A and B)** Atomic lattices in the relevant planes of (A) cuprate and (B) iron-based superconductors. Arrows depict the spin resonance associated with superconductivity in these compounds. These spin patterns are not static but fluctuate. **(C and D)** Fermi surfaces as a function of electron momentum illustrate pairing symmetries. The large squares (solid gray lines) denote the Brillouin zones (unit cells in momentum space) containing a single atom of (C) copper or (D) iron. The Fermi surfaces are denoted in blue (positive phase) and red (negative phase); for (C), the nodes (zero amplitude) occur where the blue and red arcs touch. The spin fluctuations in (A) and (B) are described by wave vectors $\mathbf{Q}_M$. **(E and F)** Phase-sensitive tests of the pairing symmetry. (E) In cuprates, quasiparticles of each phase can be separated by the macroscopic geometry of the corner junction shown. When the currents, shown by arrows, recombine, changes in their interference with applied magnetic field reveal that they exited the cuprate with opposite phase (*16*) (F) In the iron-based materials, the two phases cannot be separated by their direction, so a microscopic measurement is required to obtain phase-sensitive information. Hanaguri *et al.* used a scanning tunneling microscope to image interference effects created by magnetic vortices. Increasing interference between incoming and outgoing quasiparticles, with wave vectors $\mathbf{k}_i$ and $\mathbf{k}_f$, from the two different Fermi surfaces, shows that the phase changed sign. The difference wave vector, $\mathbf{Q}_N$, matches the spin fluctuation wave vector $\mathbf{Q}_M$ recently detected (*3*).

Insights into the pairing symmetry of the iron-based superconductors came much sooner after their discovery. Calculations by Mazin *et al.* (*7*) showed that five energy bands—plots of electron energy as a function of momentum—cross the Fermi level that separates the occupied from unoccupied electronic states (see the figure, panels B and D). These crossings, or Fermi surfaces, exhibit a "nested" structure. They have roughly the same shape but are offset from each other by a momentum that corresponds to antiferromagnetic spin fluctuations. Mazin *et al.* concluded that spin-mediated interband pairing is energetically favorable if the order parameter changes sign between the nested Fermi surfaces (*7*). Each band is individually isotropic—an *s*-wave has only one lobe and does not have a well-defined sign in isolation—but if there are several *s* bands, each can be assigned a different sign.

This "*s*±" pairing-symmetry model, the strongest candidate of the many that had been proposed, was hard to verify experimentally. Unlike the *d*-wave case, the phase change occurs not between two different momentum directions, but between two different magnitudes of quasiparticle momentum that may lie along the same direction. Macroscopic geometrical separation of the two phases, as in the cuprate corner-junction experiment, is not possible.

ARPES studies showed no nodes but could not determine phase in $NdFeAsO_{1-x}F_x$, a so-called "1111" FeAs superconductor (*8*). A detection of half-quantum magnetic flux in a loop between $NdFeAsO_{1-x}F_x$ and conventional superconducting niobium showed a phase change in the order parameter (*9*). Combining these two experiments proved the *s*± symmetry in this material, but not the pairing mechanism. A neutron scattering experiment on a related "122" FeAs superconductor, $Ba_{0.6}K_{0.4}Fe_2As_2$, detected a resonant spin fluctuation that arose only in the superconducting state, at exactly the nesting wave vector to take advantage of the *s*± symmetry (*10*) (see the figure, panels B and D).

However, the universality of these results for high-T_c iron-based superconductors has been questioned. Another family of iron materials, showing superconductivity up to 14 K (37 K under pressure), is based not on arsenic but on sulfur, selenium, and tellurium (*11*). The band structure in $FeSe_xTe_{1-x}$ appeared similar (*12*), but neutron scattering showed that the dominant static magnetic order in the parent FeTe compound is not the nesting wave vector (*13*). Combined with the absence of a spin-density-wave gap (*12*), these results fueled speculation that the superconducting mechanism was entirely different in the two families.

Further exploration of $FeSe_xTe_{1-x}$ uncovered more similarities. A spin resonance occurring at the expected nesting vector turns on just as the material enters the superconducting state (*3*). Half of the pairing mechanism—the existence of the spin mediation—was now in place, but did the Fermi surfaces in $FeSe_xTe_{1-x}$ have appropriate signs to allow pairing?

Studies of pairing symmetry must measure momentum, so Hanaguri *et al.*'s use of scanning tunneling microscopy (STM), which measures the positions of electronic states with atomic resolution, seems an unlikely choice. However, STM has provided a wealth of momentum information on the cuprates from quasiparticle interference imaging (*14*). Several types of disorder in a material can elastically scatter a quasiparticle, changing its momentum but not its energy. The initial and final quasiparticle states interfere and create a ripple in the density of states whose period is set by the difference in their momenta (see the figure, panel F) Not only can the momenta of the original, unscattered quasiparticle states be deduced, but the amplitudes of these ripples can reveal

the phase difference between incoming and outgoing quasiparticle waves.

Hanaguri *et al.* applied a magnetic field to introduce a new type of sign-changing scattering center, a superconducting magnetic vortex. As the magnetic field was increased, the quasiparticle scattering was increasingly dominated by these vortices. An increase in the amplitude of interference between quasiparticles from the two different Fermi surfaces was seen relative to interference between quasiparticles from the same Fermi surface, showing that the two different Fermi surfaces must have opposite sign.

High-T_c superconductor research has focused both on fundamental understanding and on practical applications. Thus, it is ironic that the magnetic vortices used to better understand high-T_c superconductivity are also the primary impediment to applications due to their unwanted dissipative motion when current is applied. So far, the vortices appear to be well-pinned in iron-based superconductors (*15*), but T_c has maxed out at 57 K. However, the recent evidence (*2*, *3*) establishing the spin-mediation as a leading candidate for the pairing mechanism that operates across the major families of high-T_c iron-based superconductors also provides insight into the mechanism of cuprate superconductivity. This result also suggests a promising avenue in the search for higher T_c materials—look for materials with similar band structures that undergo magnetic interactions (*5*)

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ARCHAEOLOGY

People, Societies, and Landscapes

Sophisticated geographical models are aiding archaeological research into how people have used and altered local landscapes.

Charles French

Ever since humans domesticated plants and animals, they have wielded the potential to substantially change the shape of the landscape. But more often than not, landscape change is driven not just by human activity but also by underlying factors such as climate and soil type. In the long-term interactions among people, society, and landscape, any one factor—including climate—may be responsible for tipping a system into instability. Archaeologists increasingly use advanced geographical modeling techniques to unravel these complex interactions at a community or farmstead scale (*1*–*4*).

Conventional archaeological field surveys typically provide very detailed local information, but it can be difficult to interpret these "point finds" within a larger context. Today, archaeologists use a wide range of multidisciplinary scientific techniques to investigate human-landscape interactions. Transects across and through buried landscapes are examined for their past soil and vegetation records and are combined with the spatial organizational data from the archaeological record to give detailed sequences of human intervention in the landscape (*5*, *6*).

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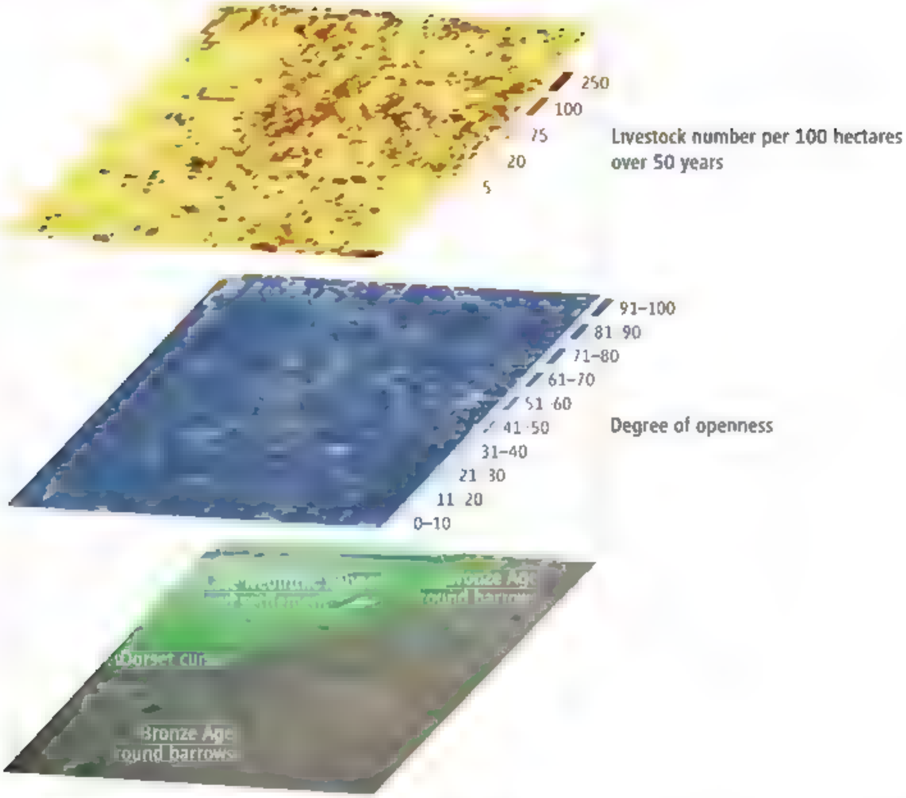
For example, in the Aguas Valley in southeast Spain, investigations using this suite of methods indicated that the advent of metalwork production with associated intensive wheat cultivation in the third millennium B.C.E. led to the start of widespread erosion, affecting the hill slopes and filling the wide alluvial floodplain with eroded soil to a depth of several meters (*7*). These events coincided with the beginning of a longer-term trend of increasing aridity and punctuated erosive landscape disruption, such as gully incision, soil erosion, and river course changes

Nonetheless, this agriculturally based proto-urban society persisted in a gradually desertifying landscape through the use of suitable land management strategies: Its people captured water in cisterns, used trickle irrigation, exploited the floodplain margins for agricultural production, and eventually terraced hillsides during Moorish times (some 500 years ago). These soil conservation measures curtailed erosion, retained dwindling moisture levels, and—until very recently—made subsistence agriculture possible. For the past two decades, tourism-related development, water abstraction, and monoculture farming and field amalgamation have led to severe surface instability, dramatic gully incision, and soil and sediment erosion, denuding large areas to a desert-like state.

In highland Yemen, Wilkinson (*8*) observed the drying out of lakes by ~5000 B.C.E. and generally drier conditions from ~3000 B.C.E.; this coincided with settlement expansion into the highland hinterlands and concomitant soil erosion. Climate data from deep-sea cores suggests that rainfall was also changing from a moist, lengthy springtime rainy season to less frequent but more intense winter rainstorms. These factors combined to intensify soil erosion, flooding, and soil accumulation in low-lying areas downstream. Nonetheless, subsistence farming has remained sustainable in these hinterland valleys until today without the use of deep-well irrigation, through land use practices such as small embanked fields, shallow plowing, and crop rotation under the current lower-rainfall regime.

A scenario similar to that of hinterland Yemen had been envisaged for the highland Ethiopian landscape across the Red Sea at Aksum (*9*). But recent geoarchaeological studies, combined with intensive archaeological field surveys, have indicated that major disruption and erosion of this landscape probably did not occur until the past few hundred years, despite the longer-term trend of aridification and the intensive settlement and agricultural base associated with the Aksumite Kingdom from ~400 B.C.E. to 1200 C.E. (*9*).



Beyond data visualization. In a dynamic GIS-based simulation, archaeological and environmental data are combined to understand landscape change. For example, the prehistoric sites of the Wyke Down area of Cranborne Chase, Dorset (**bottom**) have been studied in this way. Pollen data provide information on arboreal cover for the same area in the later Neolithic (**middle**), showing that there was 64% open ground. GIS modeling provides information on the grazing intensity required to keep the landscape at this level of openness (**top**).

Computer modeling of past landscapes can enhance and alter our perception of dynamic people-landscape interactions in the archaeological record (*10–12*). For example, the universal soil loss equation (USLE) and geographic information system (GIS) modeling have been used to investigate how Roman agriculture may have affected erosion in the Troina Valley of north central Sicily (*1*). The results suggest that greater clearance for winter pasture land was the major driving force in intensifying soil erosion.

Another approach is to use dynamic spatial models commonly used in landscape ecology to test how landscapes have changed in the past. Samarasundera has used this approach to study the upper Allen Valley of Cranborne Chase in the chalklands of southern England (see the figure) (*2*). He used well-dated, repeated, and spatially related archaeological, paleosol, palynological, and mollusk data, as well as data on livestock grazing behavior and ecological succession scenarios, to develop a range of landscape use models for the Neolithic period (from ~9500 to 3500 years ago). He concluded that livestock grazing could have caused and maintained forest recession in the early Neolithic. This is a plausible alternative to theories of arable intensification for the extensive use and exploitation of the downlands in the late Neolithic and Early Bronze Ages, as suggested hitherto (*13*, *14*).

Barton *et al.* (*3*, *15*) have further applied and developed USLE and GIS modeling with their use of a geographic resource analysis and support system (GRASS) to model Neolithic subsistence land use practices in the Wadi Ziqlab drainage of northern Jordan. The authors used raster cell sets of topography, soils, vegetation, and regional climate data to investigate alternative scenarios of long-term landscape–land use dynamics. The study suggests two alternative scenarios of landscape development: disaggregation from village to small hamlet, and grazing dominating over cultivation.

The work (*3*, *15*) successfully builds on a recent legacy of applying GIS-based modeling to archaeological landscapes (*4*, *11*), but aims to take the process one step further to explore human decision-making. This approach will not only enable comparisons between long-term landscape dynamics and the archaeological record; it also provides the tools for further testing of human-environment interactions in different landscape settings and at different scales of human activity, from household to field to valley-wide.

Where comprehensive sets of well-dated and spatially related archaeological and paleoenvironmental data are available, the use of GIS-based modeling platforms is undoubtedly a productive way forward. Such paleoecological modeling can go beyond testing archaeological hypotheses that "play out" possible realities. Rather than merely providing simple data visualizations, it can combine different sets of data and allows the interrogation of many possible scenarios of change (*16*). Detailed understanding of long-term human impacts on landscapes is thus achievable, especially when coupled with precise climate data.

Furthermore, the simulations can link past, present, and future environmental data sets, allowing the prospect of assessing current and potential future human impacts on our environment. Perhaps this is an imperative given our current fragile and unpredictable times, but modeling is no absolute substitute for good paleoenvironmental data directly related to human activities in well-understood culturally shaped landscapes.

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INTRODUCTION

Learning to Read, Reading to Learn

HOW OFTEN HAVE YOU HAD YOUR EYES PASS OVER A TEXT, ONLY TO REALIZE SOME TIME later that you absorbed nothing of it? Or spent an hour listening at a seminar, only to walk away unclear about what the most important advance was? Is this entirely your fault, or is the design of the text or the seminar partly to blame?

In this special issue, we have collected a variety of articles that focus on literacy in science. The term represents two angles of the problem: knowing what science has discovered and being able to communicate in the language of science. And the value is twofold, as well: Good literacy skills make it easier to learn science, but science topics can also be used to teach literacy skills that will translate well to other subjects.

As Snow points out (p. 450), the language used in science is different from the language used in everyday conversation. The focus on details, the exclusion of ambiguous interpretations, and the complexity of the vocabulary all present the reader with challenges different from those found in fictional texts. But as van den Broek discusses (p. 453), strategies taken by the writer or speaker can help the novice through the language barrier. Webb (p. 448) discusses the kinds of supports that are helpful when the language of school is not the native language of the students. Krajcik and Sutherland (p. 456) analyze how scientific texts are best used in a classroom setting and how to design curricula that support life-long science literacy skills. Taking the view that not all literacy is about writing, Osborne (p. 463) discusses how argumentation skills are critical for understanding why some ideas are wrong and others right. Pearson and colleagues (p. 459) describe the integration of literacy and science training through professional development for teachers, innovative curricula, and enhanced classroom materials. And research reported by Taylor *et al.* (p. 512) analyzes how both genetics and the teachers available affect a child's literacy skills.

In the Education Forum, Schleicher (p. 433) discusses how literacy skills required for participation in increasingly sophisticated societies have evolved and how meaningful international assessments can be conducted. In the 20 and 27 April issues, *Science Signaling* presents a set of Teaching Resources by Thatcher, each of which is a pair of short animations of a canonical signaling pathway; student-authored Journal Clubs cover topics ranging from signaling in cells of the immune system to signaling in plants.

Science is about generating and interpreting data. But it is also about communicating facts, ideas, and hypotheses. Scientists write, speak, debate, visualize, listen, and read about their specialties daily. For students unfamiliar with the language or style of science, the deceptively simple act of communication can be a barrier to understanding or becoming involved with the science.

— PAMELA J. HINES, BRAD WIBLE, MELISSA MCCARTNEY

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Science

PERSPECTIVE

Science Education and Literacy: Imperatives for the Developed and Developing World

Paul Webb

This article explores current language-based research aimed at promoting scientific literacy and examines issues of language use in schools, particularly where science teaching and learning take place in teachers' and learners' second language. Literature supporting the premise that promoting reading, writing, and talking while "doing science" plays a vital role in effective teaching and learning of the subject is highlighted. A wide range of studies suggest that, whether in homogenous or language-diverse settings, science educators can make a significant contribution to both understanding science and promoting literacy.

There is concern around the apparent inability of science education to counter current negative perceptions of science in both developing and industrial countries (*1*). These concerns have resulted in consensus within the science education community over the past five decades that there is a need to focus on science literacy. The framework within which this consensus initially developed emphasized scientific knowledge and applications. However, a more recent consensus that has emerged within sectors of the science education community is the need to focus more on the literacy aspects of science literacy (*2*, *3*). Norris and Phillips (*2*) draw a distinction between the fundamental and derived senses of science literacy in that the fundamental sense requires proficiency in science language and thinking, whereas being proficient in the derived sense means being able to make informed judgements on scientific societal issues (*4*).

A number of researchers (*2*, *5*) believe that for someone to be judged scientifically literate in both the fundamental and derived senses, he or she must be first proficient in the discourses of science, which include reading, writing, and talking science. In order to achieve these goals, students must be helped to cross the borders between the informal language they speak at home and the academic language used at school, particularly the specialized language of science (*5*). Furthermore, there are many situations where the teaching and learning of science takes place in a second or foreign language. Many previously Anglophone colonial states in Africa choose English as the language of teaching and learning in their schools because it is seen as the language that best provides access to economic and social mobility. In these and many other countries, issues of language are exacerbated by the fact that often both teachers and learners are second-language speakers in terms of the language of teaching and learning in their schools (*6*). It is within the above contexts that this paper reviews language-based strategies aimed at promoting science literacy.

Fig. 1. (Top) Writing to learn science. **(Bottom)** When the light goes on: thinking about science.

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Integration of Language and Science Studies

The uncritical belief that hands-on science activities automatically lead to understanding has been replaced with the realization that this is a necessary, but not sufficient, approach. What is needed are minds-on experiences that include discussion, planning, reading, and writing, as well as deliberations and argumentation. One of the first programs that explored the integration of language and science instruction introduced a science-content reading program emphasizing inquiry activities, science processes, and the comprehension of written information provided for the topic at hand (*7*). The result was that both reading and science scores improved, as well as student attitudes toward science. Further efforts, which included science writing in a large number of elementary and middle schools in two very large school districts, resulted in similar findings (*8*, *9*). Other researchers have also shown the value of reading to learn science. Cervetti *et al.* (*10*) built and tested a curriculum that used literacy instruction to help students acquire the knowledge, skills, and dispositions of inquiry-based science, an approach that also saw students making significant gains in terms of both literacy and science.

In the El Centro district in California, a science kit based writing program was developed for low socioeconomic elementary schools with a high percentage of English second-language learners (*11*). The results of a large-scale study (over 1100 students) revealed significant improvements in grades four and six science achievement and grade six writing in English. In another study (*12*), professional development was provided that integrated literacy, science, and mathematics across five school districts. The grade five students of teachers who participated in this program achieved higher scores for reading, writing, mathematics, and science, and it was shown that improved student performance was significantly affected by teacher beliefs and classroom practices. Hand (*13*) used an approach that required learners to pose questions, make claims supported by evidence, consult with experts, and reflect on changes that they made to their original thinking. The Science Writing Heuristic (SWH) approach represents a move from laboratory work as recipes and simple report writing to meaningful writing toward sense making by integrating understandings of the nature of science, scientific inquiry, and issues of argumentation. Hand's (*13*) research showed great benefits to students, and a meta-analysis of six quantitative studies (*14*), as well as a meta-synthesis of 10 qualitative studies (*15*), revealed consistently positive evidence for the SWH ap-

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proach across science topics and at all educational levels (primary school to university).

Science and Second-Language Learners

Research has shown that in developed countries real benefits accrue from developing native language literacy when working with English-language learners (*6*, *16*). There is evidence that, where the home language is neglected in favor of a second language such as English, young learners develop neither language sufficiently (*17*). Similarly, in previously colonized African and Asian societies, where the teaching and learning of science often takes place in a second or foreign language for both teacher and learners, the use of an unfamiliar European language often results in restricted teaching methods and poor student achievement (*18*). Conversely, when Haitian-Creole students were encouraged to use the vernacular to discuss topics in science, both their conceptual understandings and their capacity to recognize established relationships between claims and evidence improved (*19*).

In the South African context, where most parents and teachers tend to choose English instruction for their children because it is perceived to be the language of socio-economic power and mobility, the teachers do most of the talking while children understand little and remain silent and passive (*16*). These children's performance in national and international tests of science, literacy, and numeracy is exceptionally poor (*17*). In contrast, studies in Nigeria and Zambia have revealed that better results were produced in schools where mother tongue instruction was continued until secondary level and have shown that too early an emphasis on English impairs children's subsequent learning (*18*). Consistently poor South African results, as well as well-researched arguments around language use in schools, have stimulated South African studies that investigated the talking, writing, and arguing aspects of science in elementary and middle schools (Fig. 1). These investigations included research on classroom discussion (*20*), use of the "science notebook" approach (*21*), and argumentation (*22*). All of the studies incorporated the use of students' native language and produced encouraging results in terms of improved problem-solving, science, and argumentation skills, respectively.

These South African findings resulted in the development of an approach (*23*) that aimed to integrate reading to learn science and learning to read for science; exploratory talk toward investigable questions, planning, and doing an investigation; and scaffolded writing to learn science, argumentation, and critical thinking. The basic tenets of the model are illustrated in Fig. 2.

The stimulus (the reading material, discrepant, or unexpected event, etc.) provides the stimulation for discussion but can also help access information needed to raise investigable and researchable questions. The discussion and the investigable question generated provide the framework for planning and executing the investigation, whereas the data generated are recorded in a science notebook (*24*). Once the line of learning is drawn in the children's science notebook—that is, they have drawn all the conclusions that they can from their classroom investigation—further reading and research allows them to go beyond the limits of their investigatable question. This means that they can explore the noninvestigatable but researchable questions that were raised as part of their earlier discussions through other forms of information gathering. Lastly, getting students to record their arguments within an argumentation writing frame provides an exercise that aims to improve their understandings of the nature of science, scientific processes and procedures, and notion of audience and presentation. When teachers were trained to use the model, issues of bilingualism and code switching were discussed, and they were encouraged to make explicit to their students that they could legitimately discuss, argue, and write in their home language while doing a scientific investigation (*23*).

The model was implemented with grade six teachers and learners in a deep rural area of South Africa where, although the language of teaching and learning in these schools is English, the children and parents rarely hear or speak the language. The results of this 1-year intervention mirrored those of the earlier South African studies described above, but new findings were that the students' English reading skills improved significantly, as did their writing and listening skills in their native language (*23*).

Language and Learning

There are a number of research findings, both in the developed and developing world, that show the benefits of native language instruction for English-language learners (*25*, *26*). In terms of science education, it is suggested that for successful learning to take place attention must be paid to cognitive development in both the language of instruction and the students' native language. One such way of doing this is by teachers code-switching (when possible) and/or allowing children to first make sense of what is expected of them in their home language and then to translate what they understand into the official language of teaching and learning. In turn, there is growing support for the premise that promoting reading, writing, and talking while "doing science" plays a vital role in effective teaching and learning of the subject. In the final analysis, what is important is that, whether in homogenous or language-diverse settings, science educators can make a significant contribution to both understanding science and promoting literacy. As such, they should be encouraged to pay closer attention to

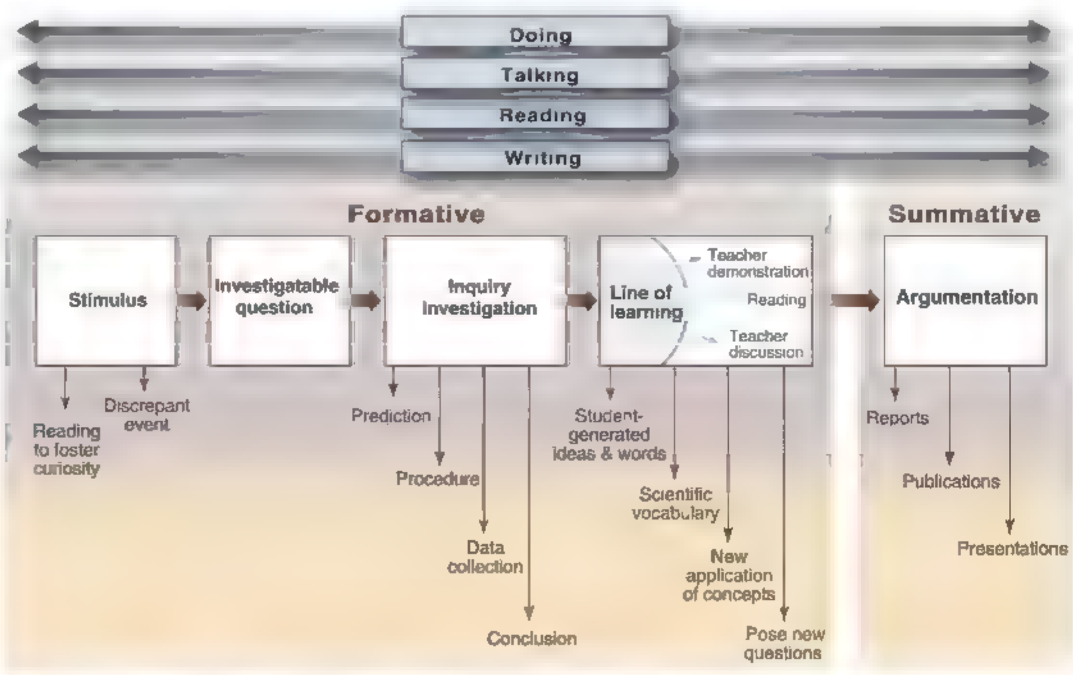

Fig. 2. An integrated strategy for promoting teaching and learning toward scientific literacy.

their learners' struggles to come to terms with unfamiliar language, discourse patterns, and the often formidable conventions of science (*27*).

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PERSPECTIVE

Academic Language and the Challenge of Reading for Learning About Science

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A major challenge to students learning science is the academic language in which science is written. Academic language is designed to be concise, precise, and authoritative. To achieve these goals, it uses sophisticated words and complex grammatical constructions that can disrupt reading comprehension and block learning. Students need help in learning academic vocabulary and how to process academic language if they are to become independent learners of science.

Literacy scholars and secondary teachers alike are puzzled by the frequency with which students who read words accurately and fluently have trouble comprehending text (*1*, *2*). Such students have mastered what was traditionally considered the major obstacle to reading success, the depth and complexity of the English spelling system. But many middle- and high-school students are less able to convert their word-reading skills into comprehension when confronted with texts in science (or math or social studies) than they are when confronted with texts of fiction or discursive essays. The greater difficulty of science, math, and social studies texts than of texts encountered in English language arts (mostly narratives) suggests that the comprehension of "academic language" may be one source of the challenge. So what is academic language?

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Academic language is one of the terms [others include language of education (*3*), language of schooling (*4*), scientific language (*5*), and academic English (*6*, *7*)] used to refer to the form of language expected in contexts such as the exposition of topics in the school curriculum, making arguments, defending propositions, and synthesizing information. There is no exact boundary when defining academic language; it falls toward one end of a continuum (defined by formality of tone, complexity of content, and degree of impersonality of stance), with informal, casual, conversational language at the other extreme. There is also no single academic language, just as there is no single variety of educated American English. Academic language features vary as a function of discipline, topic, and mode (written versus oral, for example), but there are certain common characteristics that distinguish highly academic from less academic or more conversational language and that make academic language—even well-written, carefully constructed, and professionally edited academic language—difficult to comprehend and even harder to produce (*8*).

Among the most commonly noted features of academic language are conciseness, achieved by avoiding redundancy; using a high density of information-bearing words, ensuring precision of expression; and relying on grammatical processes to compress complex ideas into few words (*8*, *9*). Less academic language, on the other hand, such as that used in e-mails, resembles oral language forms more closely: Most sentences begin with pronouns or animate subjects; verbs refer to actions rather than relations; and long sentences are characterized by sequencing of information rather than embeddings. The two excerpts in Fig. 1, both about torque (a topic included in many state standards for 7th-grade science), display the difference between a nonacademic text (from the Web site www.lowrider.com) and an academic text (from the Web site www.tutorvista.com).

A striking difference between more informal and more academic language exemplified in the Lowrider/TutorVista text comparison is the greater presence of expressive, involved, interpersonal stance markers in the first Lowrider posting ("…guys get caught up…," "I frequently get asked…," "Most of us…") and in the response

From http://www.lowrider.com/forums/10-Under-the-Hood/topics/183-HP-vs-torque/posts (spelling as in the original posting)

Often times guys get caught up in the hype of having a big HP motor in their lolo. I frequently get asked whats the best way to get big numbers out of their small block. The answer is not HP, but torque. "You sell HP, you feel torque" as the old saying goes. Most of us are running 155/80/13 tires on our lolo's. Even if you had big HP numbers, you will "never" get that power to the ground, at least off the line. I have a 64 Impala SS 409, that i built the motor in. While it is a completely restored original (I drive it rolling on 14" 72 spoke cross laced Zeniths), the motor internals are not. It now displaces 420 CI, with forged pistons and blalanced rotating assembly. The intake, carb and exhaust had to remain OEM for originality's sake, and that greatly reduces the motors potential. Anyway, even with the original 2 speed powerglide, it spins those tires with alarming ease, up to 50 miles per hour!

In my 62, I built a nice 383 out of an 86 Corvette. I built it for good bottom end pull, since it is a lowrider with 8 batteries. And since it rides on the obligitory 13's, torque is what that car needs. It pulls like an ox right from idle all the way up to its modest 5500 redline. But I never take it that high, as all the best power is from 1100 to 2700 RPM.

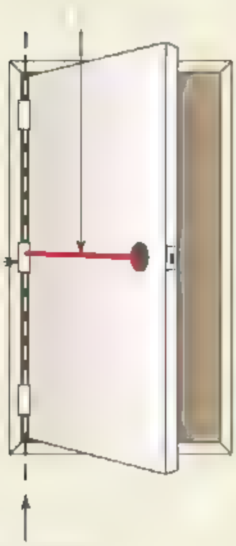
So when considering an engine upgrade, look for modifications that improve torque. That is what your lolo needs!

Posted by Jason Dave, Sept 2009

Jason you are right on bro. I have always found an increase in torque placement has not only provided better top end performance but also improved gas mileage in this expensive gas times.

Posted by Gabriel Salazar, Nov 2009

From http://www.tutorvista.com/content/physics/physics-iii/rigid-body/torque.php



Torque is the product of the magnitude of the force and the lever arm of the force.
What is the significance of this concept in our everyday life?

Dependence of torque on lever arm
To increase the turning effect of force, it is not necessary to increase the magnitude of the force itself. We may increase the turning effect of the force by changing the point of application of force and by changing the direction of force.

Let us take the case of a heavy door. If a force is applied at a point, which is close to the hinges of the door, we may find it quite difficult to open or close the door. However, if the same force is applied at a point, which is at the maximum distance from hinges, we can easily close or open the door. The task is made easier if the force is applied at right angles to the plane of the door.

When we apply the force the door turns on its hinges. Thus a turning effect is produced when we try to open the door. Have you ever tried to do so by applying the force near the hinge? In the first case, we are able to open the door with ease. In the second case, we have to apply much more force to cause the same turning effect. What is the reason?

The turning effect produced by a force on a rigid body about a point, pivot or fulcrum is called the moment of a force or torque. It is measured by the product of the force and the perpendicular distance of the pivot from the line of action of the force.

Moment of a force = Force x Perpendicular distance of the pivot from the force

The unit of moment of force is newton metre (N m).
In the above example, in the first case the perpendicular distance of the line of action of the force from the hinge is much more than that in the second case. Hence, in the second case to open the door, we have to apply greater force.

Fig. 1. Examples of nonacademic text (Lowrider, top) and academic text (TutorVista, bottom).

("Jason you are right on bro"). Though both the Lowrider authors are writing to inform, they are not assuming the impersonal authoritative voice that is characteristic of academic language. They claim their authority to provide information about the advantage of torque over horsepower adjustments on the basis of personal experience. The scientist's authoritative stance, on the other hand, derives from membership in a community committed to a shared epistemology; this stance is expressed through a reduction in the use of personal pronouns, a preference for epistemically warranted evaluations (such as "rigorous study" and "questionable analysis") over personally expressive evaluations (such as "great study" and "funky analysis"), and a focus on general rather than specific claims. Maintaining the impersonal authoritative stance creates a distanced tone that is often puzzling to adolescent readers and is extremely difficult for adolescents to emulate in writing.

Perhaps the simplest basis for comparing the Lowrider and TutorVista texts is to consider how rare in other contexts are the words they use most

frequently. The rarest words used in the Lowrider text are the special term "lolo" and its alternative form "lowrider," "upgrade," "carb," "HP," "exhaust," "spin," and "torque." Only two words from the Academic Word List (*10*), a list of words used frequently across academic texts of different disciplines, appear in this passage. The TutorVista text rare words include "magnitude," "perpendicular," "lever," "pivot," "hinge," "fulcrum," and "torque," and it uses the academic words "task," "maximum," "significance," and "illustration." The difference in word selection reflects the convention in the more academic text of presenting precise information in a dense, concise manner.

Nominalizations are a grammatical process of converting entire sentences (such as "Gutenberg invented the printing press") into phrases that can then be embedded in other sentences (such as "Gutenberg's invention of the printing press revolutionized the dissemination of information"). Nominalizations are crucial to the conciseness expected in academic language. In the TutorVista sentence "We may increase the turning effect of the force by changing the point of application of force and by changing the direction of force," "application" and "direction" are nominalizations representing entire propositions. "Application" is shorthand for "where we apply," and "direction" is shorthand for "how we direct." Thus, although this sentence has the same apparent structure as "We can get a smile from a baby by changing his diaper and by patting his back," the processing load is much higher. "Increase" in the original sentence is a verb referring to a relation between two quantities, whereas "get" in the baby-sentence adaptation refers to an action or effect in the real world. "Diaper" and "back" are physical entities subjected to actions, whereas "application" and "direction" are themselves actions that have been turned into nouns. Part of the complexity of academic language derives from the fact that we use the syntactic structures acquired for talking about agents and actions to talk about entities and relations, without recognizing the challenge that that transition poses to the reader. In particular, in science classes we may expect students to process these sentences without explicit instruction in their structure.

Science teachers are not generally well prepared to help their students penetrate the linguistic puzzles that science texts present. They of course recognize that teaching vocabulary is key, but typically focus on the science vocabulary (the bolded words in the text), often without recognizing that those bolded words are defined with general-purpose academic words that students also do not know. Consider the TutorVista definition of torque: "Torque is the product of the magnitude of the force and the lever arm of the force." Many 7th graders are unfamiliar with the terms "magnitude" and "lever"; and some proportion will think they understand "product," "force," and "arm" without realizing that those terms are being used in technical, academic ways here, with meanings quite different from those of daily life. Yet this definition, with its sophisticated and unfamiliar word meanings, is the basis for all the rest of the TutorVista exposition. the trade-off between magnitude and direction of force.

Efforts to help students understand science cannot ignore their need to understand the words used to write and talk about science: the all-purpose academic words as well as the discipline-specific ones. Of course some students acquire academic vocabulary on their own, if they read widely and if their comprehension skills are strong enough to support inferences about the meaning of unknown words (*11*). The fact that many adolescents prefer reading Web sites to books (*12*), however, somewhat decreases access to good models of academic language even for those interested in technical topics. Thus, they have few opportunities to learn the academic vocabulary that is crucial across their content-area learning. It is also possible to explicitly teach academic vocabulary to middle-school students. Word Generation is a middle-school program developed by the Strategic Education Research Partnership that embeds all-purpose academic words in interesting topics and provides activities for use in math, science, and social studies as well as English language arts classes in which the target words are used (see the Web site for examples) (*13*). Among the academic words taught in Word Generation are those used to make, assess, and defend claims, such as "data," "hypothesis," "affirm," "convince," "disprove," and "interpret." We designed Word Generation to focus on dilemmas, because these promote discussion and debate and provide motivating contexts for students and teachers to use the target words. For example, one week is devoted to the topic of whether junk food should be banned from schools, and another to whether physician-assisted suicide should be legal. Discussion is in itself a key contributor to science learning (*14*) and to reading comprehension (*15*, *16*). Words learned through explicit teaching are unlikely to be retained if they are taught in lists rather than embedded in meaningful texts and if opportunities to use them in discussion, debate, and writing are not provided.

It is unrealistic to expect all middle- or high-school students to become proficient producers of academic language. Many graduate students still struggle to manage the authoritative stance, and the self-presentation as an expert that justifies it, in their writing. And it is important to note that not all features associated with the academic writing style (such as the use of passive voice, impenetrability of prose constructions, and indifference to literary niceties) are desirable. But the central features of academic language—grammatical embeddings, sophisticated and abstract vocabulary, precision of word choice, and use of nominalizations to refer to complex processes—reflect the need to present complicated ideas in efficient ways. Students must be able to read texts that use these features if they are to become independent learners of science or social studies. They must have access to the all-purpose academic vocabulary that is used to talk about knowledge and that they will need to use in making their own arguments and evaluating others' arguments. Mechanisms for teaching those words and the ways that scientists use them should be a part of the science curriculum. Collaborations between designers of science curricula and literacy scholars are needed to develop and evaluate methods for helping students master the language of science at the undergraduate and high-school levels as well as at the middle-school level that Word Generation is currently serving.

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REVIEW

Using Texts in Science Education: Cognitive Processes and Knowledge Representation

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Texts form a powerful tool in teaching concepts and principles in science. How do readers extract information from a text, and what are the limitations in this process? Central to comprehension of and learning from a text is the construction of a coherent mental representation that integrates the textual information and relevant background knowledge. This representation engenders learning if it expands the reader's existing knowledge base or if it corrects misconceptions in this knowledge base. The Landscape Model captures the reading process and the influences of reader characteristics (such as working-memory capacity, reading goal, prior knowledge, and inferential skills) and text characteristics (such as content/structure of presented information, processing demands, and textual cues). The model suggests factors that can optimize—or jeopardize—learning science from text.

Texts support the acquisition of scientific knowledge. Schools, colleges, and universities depend on texts for their science instruction. The use of texts is not simply a matter of convenience: The subject matter usually is so abstract that detailed verbal descriptions—possibly supplemented by illustrations, videos, demonstrations, and so on—are indispensable. Given the importance of texts in science education, how is it that people learn science from text, and how can such learning be optimized?

Comprehension and Learning

The processing of texts in the context of learning requires both comprehension and learning—the incorporation of comprehended information in the reader's background knowledge. Investigations of text processing have focused predominantly on the comprehension component. Most theoretical models of comprehension agree that comprehension entails the construction by the reader of a coherent mental representation that captures the intended meaning of the text (*1*–*6*). In a successful representation, the individual elements in the text (e.g., concepts and facts about the concepts) are connected to each other by meaningful relations. The reader recruits relevant background knowledge into the representation as well. Together, the elements and relations create a "situation model," an interpreted description of the information in the text (*7*). For comprehension, the reader's background knowledge supports the process of interpreting and representing the text. For learning, background knowledge becomes the object of change. How are the reader's existing knowledge structures updated to incorporate new concepts? How are they modified when found to be inconsistent with the text? Relatively little psycholinguistic research has been conducted to answer these questions, but findings on text comprehension provide insights into processes and mechanisms involved in learning from text.

Attention Allocation and Inference Generation

Reading as a landscape of activations. The situation model depends on the identification of meaningful relations between text elements and between those elements and background knowledge. The processes by which readers identify relations, or fail to identify important relations, are captured by psychological models such as the Landscape Model (*5*, *8*). These models have been developed primarily in the context of narrative reading (fiction and storytelling) but have been found to apply to science (informational and factual) texts as well (*9*–*11*). The Landscape Model identifies the reading process as a balancing act between the reader's limited attention or working memory and the need for coherence. At any point during reading, the reader can only attend to a subset of all the elements in a text or all the relevant background knowledge (*2*). As the reader proceeds through the text, the contents of working memory are continually

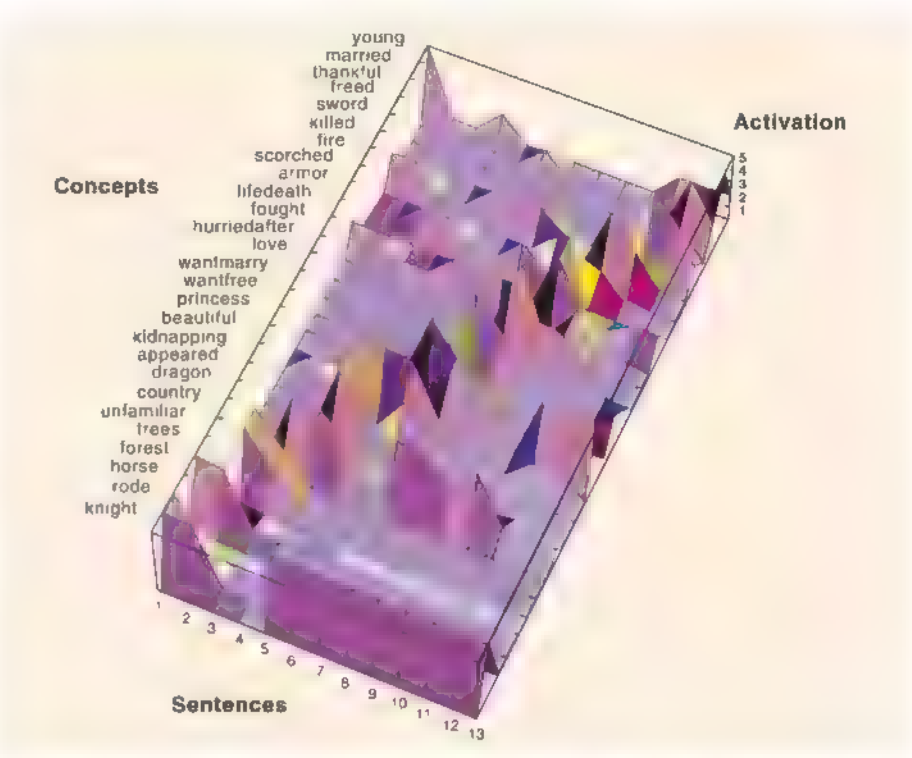

Fig. 1. Computer simulation of hypothetical activations during reading of a narrative text about a knight, a princess, and a dragon. The simulation displays the activation (vertical dimension) of text and background-knowledge elements ("concepts") over the course of reading (sentences 1 to 13). Concepts that are activated simultaneously are connected in the memory representation, with the strength of the resulting relation a function of the degree of activation of each concept. [Based on (*5*), used with permission]

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refreshed, with some elements remaining the focus of attention and others being replaced by new ones. As reading progresses, the landscape of activations of individual concepts fluctuates (Fig. 1).

Establishing coherence. The exact nature of the landscape of fluctuating activations has important consequences for the establishment of coherence because a direct relation between two elements is most likely to be detected if the two elements are simultaneously in the focus of attention of the reader and unlikely to be detected if the elements are not simultaneously activated. The limits imposed by working memory capacity and the importance of simultaneous activation for inferring relations make the reader's allocation of attention of prime importance for comprehension. Relations between elements presented far apart in the text may not be detected effectively, and the reader's misconceptions may impede comprehension because they may support incorrect relations.

Text and reader characteristics. The allocation of attention is influenced by characteristics of both text and reader. Demands on attention are affected by such text characteristics as organization, verbal complexity, and the linguistic markers or typographical prompts that cue up relations. The optimal format of texts depends on the properties of the audience. For example, readers with relevant background knowledge or good reading skills remember more from a somewhat incoherent text than from a very coherent text, whereas readers with little background knowledge or poor reading skills show the opposite pattern (*9*, *12*).

The reader's attention is influenced by the availability of working memory and of relevant background knowledge (*12*). Motivational factors such as the goal for reading the text (*9*) and skill factors such as reading and reasoning strategies (*13*) also determine what attention the reader can bring to bear on the text. These strategies and skills enable the reader to control attentional focus, to determine what types of relations exist between activated elements, and to decide whether further analysis is needed before further reading. Readers bring individual differences to reading, differences that can be measured in eye movements, speeded responses to probes, or think-aloud protocols that can predict inference generation (*14*, *15*) (Fig. 2).

Standards of coherence. The tension between limited attentional resources and the need for coherence is negotiated by the reader's standards of coherence, which reflect the reader's understanding of what sorts of relations are needed to comprehend the text (*9*). These standards influence when and with what strategies the reader will try to establish coherence (*16*). Strategies invoked might be to reactivate information from earlier text, to slow down, or to search background knowledge. In a particular reading situation, a reader's standards depend on knowledge of standards in general, the reading goals, and the type of text. Different types of text may depend on different types of relations (for example, some types of relations may be more central to narrative than to informational texts and vice versa).

Although many types of relations can exist in a text, two types of relations crucial for just about any reading situation are referential and causal/logical relations (*17*, *18*). Referential relations provide connections of identity, relating entities (e.g., persons, objects, concepts) across sentences, whereas causal/logical relations indicate how facts and events described in one sentence cause or lead to facts and events in another sentence. Consider, for example, the following pair of sentences.

The explosion caused by the giant meteor was enormous.

It contributed to the extinction of many species.

In the second sentence, the pronoun "it" refers to "explosion" in the first sentence, establishing referential coherence. The event described in the second sentence, the extinction of species, is (at least partly) caused by the fact described in the first sentence, the explosion and its aftermath.

Referential and causal/logical relations such as these are common in most texts. Other types of relations may also be recognized if the text makes them particularly salient or they are uniquely important to the topic (for example, chronological relations in a history text or spatial relations in a geometry book) or if the reader's interests focus on those relations [for example, a homebuyer and a burglar identify different relations when reading a description of a house (*19*)].

Fig. 2. Cognitive processes during reading can be investigated by eye-tracking devices. [Photo courtesy of S. Carlson, University of Minnesota]

Relations may be "signaled" by the text. In the example, the implicit causality conveyed by the verb "contributed" directs the reader toward detecting a particular semantic relation; similar functions can be performed by other means such as the use connectives (for instance, "thus"). The example also illustrates that the identification of a relation often requires background knowledge. The text indicates that a causal relation exists, but without background knowledge (for instance, the clouds caused by the explosion may lead to a drop in temperature) the exact nature of the relation will elude the reader. Indeed, having or recruiting the wrong background knowledge (for instance, that the explosion killed by direct impact) may interfere with proper comprehension. Recruiting incorrect information can interfere with detection of relations.

Texts that offer relations separated by paragraphs or pages or that require coordination of multiple pieces of information, features common to informational texts, are particularly challenging for readers.

As a reader progresses through a text, a landscape of activations unfolds. In successful comprehension, relations are detected between coactivated concepts, leading to the gradual emergence of a mental representation of the text, relevant background knowledge, and their semantic relations. Most texts outpace most readers' attentional resources. Readers with effective and efficient strategies for selective allocation of attention are more likely to identify the relations that matter, and texts that offer helpful guideposts optimize their ability to engender comprehension.

"The design of science texts affects the likelihood that new concepts or relations can be added to the reader's background knowledge."

Learning Science from Text

The processes involved in comprehending while reading a text have direct bearing on the reader's learning from the text. Both when reading a text and when learning, informational elements and their relations are incorporated in a representation of the text (in the case of comprehension) and of background knowledge (in the case of learning).

Expanding the reader's knowledge. One form of learning from text is the addition of new information to a reader's background knowledge. The "new information" may be informational elements (facts, events, or concepts) or may be new relations between elements that the reader already knew. The design of science texts affects the likelihood that new concepts or relations can be added to the reader's background knowledge. Texts that promote effective attention allocation support learning. Relations are more easily detected if the to-be-connected information is presented close together in the text, which may entail repeating previously stated information (*20*). Relation construction can be facilitated by linguistic and other markers. In the case of referential relations, for example, consistent use of the same terms (rather than synonyms) for the same concepts and unambiguous use of pronouns can assist the reader. For causal/logical relations, the use of connectives such as "thus," "as a result of," and so on facilitates relation identification. Text signals such as headers, underlining, italics, and so on likewise direct attention (*21*). Finally, the use of straightforward grammar and familiar vocabulary can minimize the amount of attention that the reader needs to divert from learning.

These aspects of the design of a science text must be balanced by the purpose of the text and the practical constraints of the publication medium. For example, if the purpose is to expand a reader's knowledge of various nomenclatures for brain regions or gene types, then referential simplification may be counterproductive. With regard to practical constraints, where space is at a premium (as in many scientific journals), repetition of concepts to facilitate relation identification may be a limited option. In such cases, one must rely on the motivation and prior knowledge of the readers to allow them to handle the increased processing demands.

Modifying the reader's knowledge. A common, albeit less obvious, form of learning from text entails the modification of existing knowledge. A reader's misconceptions are especially problematic. Not only do new elements and relations need to be added to the reader's knowledge base but conceptual change also needs to take place. Existing elements and relations need to be removed or adjusted (*22*). Modification of existing knowledge is often more difficult than acquisition of new knowledge (*11*, *23*). One strategy is to present the correct information and assume the reader will adjust any misconceptions. Unfortunately, misconceptions are resilient to this kind of strategy. Instead, conceptual change is most likely when the correct and the incorrect information are presented conjointly and identified as such (*11*, *23*).

"Modification of existing knowledge is often more difficult than acquisition of new knowledge."

Learning from text may entail both expansion and modification of the reader's knowledge base (Fig. 3). The processing of a particular text by a particular reader is the result of an interaction between text and reader properties. No text is perfect for all readers.

Coherent versus correct representations. The establishment of coherence is a necessary step toward learning from a text. However, coherence—the perception that the text "hangs together" and is consistent with one's background knowledge—does not ensure that correct learning will take place, because it is possible for a reader to create an internally coherent representation that nevertheless is an inaccurate representation of the facts (*22*).

Examples from the history of science are heliocentrism and electrical current as the flow of charged particles. Thus, the student's assessment of understanding serves as an unreliable guide by which to judge whether or not learning occurred as intended by the author.

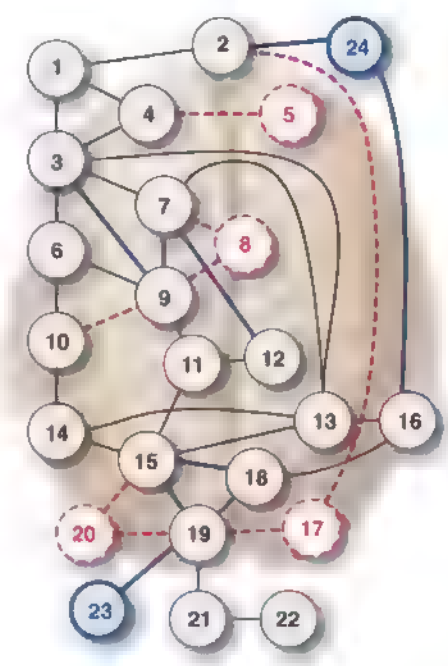

Fig. 3. Learning from text. Expansion and modification of a hypothetical reader's knowledge structure. Represented are correct prior knowledge (black), newly acquired knowledge (blue), and corrected misconceptions (red).

Using nontextual materials to supplement texts. Science texts are often supplemented by nontextual materials such as figures, diagrams, movies, or hands-on experience. Sometimes such materials are used to draw the reader into the text or to lessen the formidability of a dense page of text. At other times, they are used to support directly the expansion and modification of the reader's knowledge—often interrupting the processing of the text. To support learning, supplemental materials and activities must increase the likelihood of simultaneous activation of the to-be-related information, thereby supporting the establishment of important relations. When used judiciously, supplemental materials and activities can greatly assist science learning. However, materials and activities that are more of a distraction than an enhancement will exact a cost on comprehension. This is likely to occur, for example, when the simultaneous processing of information from multiple input channels increases cognitive load or when the nontextual information is irrelevant to the meaning of the text, as may happen when pictures are included solely to increase the attractiveness of the text.

Seductive details. Another frequently used method to increase a reader's motivation to read the science text at hand is to provide an anecdote designed to elicit the personal interest of the reader in the topic of the text. As with the use of nontextual materials, such anecdotes may indeed attain the desired goal of increasing motivation, but they pose a risk if precious attentional resources flow to processing the motivating information and away from the conceptually central information (*24*, *25*), a phenomenon known as the "seductive detail" effect. This undesired effect can be diminished by limiting and demarcating anecdotes.

Learning science from texts, learning reading from science texts. The emphasis in this article is on the transmittal of knowledge from science texts to the reader. Concurrently, the act of reading contributes to the development of reading comprehension skills. The attention allocation and inferential skills that skilled readers employ during reading are enhanced by exposure to texts that vary in structure, difficulty, and content area. Science texts differ greatly from narratives in their demands on working memory management, comprehension strategies, and the use of background knowledge. Thus, practice with science and narrative texts broadens the cognitive "toolbox" that a reader can bring to any text.

Unresolved Issues

Investigation of cognitive processes during reading has provided important insights into conditions that promote or hinder the acquisition of new knowledge from science texts. However, many unresolved issues remain. One such issue is that mere coactivation of elements in working memory cannot fully account for the learning of all scientific concepts, many of which are chains of conceptual relations too long or complex to reside in working memory under the best of circumstances. It seems likely that direct relations between a few concepts accumulate into clusters of knowledge characterized by conceptual proximity. A second issue concerns the conditions that determine whether textual information overrides a misconception that the reader holds. What does it take for a single text to modify a reader's prior knowledge? A third issue concerns the variety of types of texts. As noted, much reading research has been executed in the realm of narrative texts, less with informational texts (*26*). It is likely that the essential toolbox of cognitive processes (working memory capacity, comprehension strategies, and standards of coherence) applies to all types of text, but the specific implementation may vary as a function of text type.

Using Texts to Teach Science

Texts are frequent and powerful tools for conveying scientific facts, principles, and explanations. To be effective, however, science texts need to be designed to optimize the likelihood that learning will occur. Central to comprehension of and learning from science texts is the identification of relations among the elements in the text and between these elements and the reader's prior knowledge, processes that occur while reading. Optimally designed science texts direct the reader's landscape of activations during reading in such a way that elements that should be connected do indeed get connected. When that happens, science texts are among the most effective tools we have available to teach science, to expand readers' knowledge of scientific topics, and to correct misconceptions.

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REVIEW

Supporting Students in Developing Literacy in Science

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Reading, writing, and oral communication are critical literacy practices for participation in a global society. In the context of science inquiry, literacy practices support learners by enabling them to grapple with ideas, share their thoughts, enrich understanding, and solve problems. Here we suggest five instructional and curricular features that can support students in developing literacy in the context of science: (i) linking new ideas to prior knowledge and experiences, (ii) anchoring learning in questions that are meaningful in the lives of students, (iii) connecting multiple representations, (iv) providing opportunities for students to use science ideas, and (v) supporting students' engagement with the discourses of science. These five features will promote students' ability to read, write, and communicate about science so that they can engage in inquiry throughout their lives.

Systematic investigation of meaningful questions about natural phenomena and the development of evidence-based explanations form the foundations of science inquiry (*1*, *2*). In classrooms that emphasize such inquiry, fundamental literacy practices such as reading, writing, and oral discourse are essential to developing an understanding of the core ideas of science.

The National Science Education Standards (*1*) define scientific literacy as the understanding of science content and scientific practices and the ability to use that knowledge to participate in decision-making that is personal or that affects others in a global community. In addition, the Standards state that scientific literacy requires the ability to critique the quality of evidence or validity of conclusions about science in various media, including newspapers, magazines, television, and the Internet. The American Association for the Advancement of Science stresses the importance of scientific literacy for citizens' ability to participate with others in a global society (*3*). Underlying all of these definitions is the understanding that students must read, write, and communicate effectively to make decisions as informed citizens and engage in the critical thinking that active science learning requires. We have selected five aspects from the many features of literacy that are important to embed in inquiry science: (i) linking new ideas to prior knowledge and experiences, (ii) anchor-

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ing learning in questions that are meaningful in the lives of students, (iii) connecting multiple representations, (iv) providing opportunities for students to use science ideas, and (v) supporting students' engagement with the discourses of science. These five principles, discussed herein, are relatively consistent with the findings of others, and they repeatedly surface in our research in classrooms across the country (Table 1).

The first feature that promotes literacy as students engage in inquiry is linking new knowledge to prior knowledge. Prior knowledge forms a cornerstone of all subsequent learning, and eliciting prior knowledge becomes especially important when concepts are abstract, when scientific principles seem distant from students' everyday lives, and when students' experiences lead them to develop inaccurate ideas (*4*, *5*). For instance, middle school students may think of air as not made of anything, and because they conceptualize it as nothingness, they struggle to understand air as matter. However, students know that they have to add air to a basketball to make it bounce. Unfortunately, science instruction and curriculum materials often fail to explicitly link students' prior knowledge and experiences to new learning (*6*). When instruction does not elicit experiences with air and familiar objects, students lack foundational understanding that can support them in learning that all matter, including air, is particulate.

Prior knowledge can come from either real-world experiences or previous classroom learning. The opportunity to share and connect ideas to build on them is key to constructing understanding. For example, consider the challenging concept of convection. Once students develop an initial understanding of energy and of matter as particulate, they are prepared to develop a coherent conceptual understanding of convection built on ideas already learned (*7*, *8*). Record-keeping of new understandings as they develop (such as in an individual science journal or a shared class bulletin board) becomes central to the ability to reflect on and connect ideas across time. Figure 1, taken from a sixth-grade chemistry unit (*9*), illustrates how reading materials help students connect in-class experiences with new information and generalize from those experiences to understand scientific principles. The materials suggest that students read, write, and discuss connections, using all three literacy practices to make sense of science content and to build understanding (*7*) as they investigate whether air has mass and volume.

A second important aspect of instruction and materials design for literacy in science is that to support students' exploration of phenomena, writing about science, and reading of science text, instruction needs to be driven by questions that learners find meaningful and engaging. When learning is driven by a need to know, individuals put forth effort to understand difficult material (*10*). Motivating questions that connect to their lives help students set a purpose for engaging in scientific inquiry, as well as in the practices of reading and writing to learn. For instance, a question such as "Can good friends make me sick?" can motivate the study of the immune system and what causes diseases.

Although questions can serve to motivate learners' engagement in both first- and secondhand investigations (*11*), many students remain unengaged by the expository text common to scientific literature and textbooks. Studies have shown that the vocabulary, complex sentence structures, use of passive voice, and other elements of scientific discourse prove challenging for many readers (*7*, *12*–*14*) and may contribute to students' waning interest in learning science. Given that reading is of critical importance in science, those who struggle to read scientific texts are limited in the depth of understanding they can construct (*15*) and in their ability to engage in inquiry.

Posing interesting questions that motivate students to seek answers is one way to support their engagement (*10*), as the need to know drives text-based, as well as hands-on, investigation. For example, students are familiar with many chemical reactions in their everyday lives that they are not likely to recognize as chemical reactions. Raising related questions that students wonder about (such as "What makes fireworks different colors?" or "Why do people cry when they peel onions?") might interest them in learning about chemical reactions in a way that seeing "Chapter 3: Chemical Reactions" in a textbook might not. These questions, along with original, student-generated questions, foster motivation to explore. As students progress in school, content-based questions (such as "How can two materials have the same chemical composition and molecular mass but have very different properties?") might motivate students more than announcing "Today we begin studying isomers."

Investigating the answers to questions that students find meaningful is important in the inquiry classroom, in which students experience phenomena and questions naturally stimulate learning. Using questions in the curriculum and encouraging them in instruction illustrates for students the manner in which scientists begin their own inquiry by defining the boundary between what is known and what is unknown (Fig. 1). Similarly, question-asking plays an important role in reading scientific text, as questions can establish a purpose for reading that guides comprehension. In setting a purpose for reading, questions affect which details individuals focus on and remember as they read. Scientific texts that employ questions as headers and instruction that models the use of questions to drive classroom activities can cultivate engagement and comprehension with scientific text (*16*).

Questions serve three important roles in the science classroom. First, questioning plays a critical role in science-content learning, as it sets a need to know that drives in-class or textual investigation. Second, questioning supports literacy development for science learning, as it helps to establish a purpose for reading and to guide comprehension of written text. Last, but equally as important, questioning engages students in a key scientific-inquiry practice, as scientists also initiate the discovery process by asking questions.

Given the complexity of many scientific ideas, a third important aspect of developing literacy in science is the ability to make sense of models, maps, diagrams, simulations, and graphs. It is difficult to explain the structure of DNA with text only, and a model of the double-helix is equally difficult to understand without text that explains it. Integrating text and representations

Table 1. Fostering literacy in the context of science inquiry.

Name	Description
Link to prior knowledge and experiences	Connect science ideas with students' everyday experiences and with previous classroom experiences
Anchor in questions	Articulate questions that are meaningful and important to the lives of learners
Integrate text and visual representations	Explicitly reference visual elements in written text, and teach students to use graphics and text to support meaning making
Make use of ideas	Provide students with time, opportunities, and guidance to apply science learning to new contexts
Engage in the discourses of science	Explicitly support scientific discourses, including the language of science and its practices

(*17*) enables the structure and function of DNA to become more readily comprehensible for readers.

Curriculum materials that integrate text and graphics can help middle school students understand complex topics such as the relation between temperature and the movement of particles (Fig. 1). The enumerated list below the drawing in Fig. 1 focuses attention on particular elements of the visual representation to encourage students to look back and forth between the text and graphics. For further instructional support, teachers can model the practice of looking back and forth between text and representation by reading aloud, illustrating this practice for students.

In addition, as we move further into an age of ubiquitous technologies and the use of graphics becomes more widespread, the options for visual, auditory, and tactile interaction become greater, and the need to integrate information across multiple forms of representation increases (*18*). Instead of a static representation of kinetic molecular theory as shown in Fig. 1, students could view a dynamic simulation illustrating the movement of gas particles at different temperatures. Although such interactive features are likely to promote learning by addressing the variety of ways that people learn, the need to learn how to read such representations remains.

A fourth important element that supports the development of scientific literacy depends on curriculum and instruction that asks students to actively apply ideas to new contexts (*19*, *20*). Materials and instruction need to provide students with time, opportunities, and guidance to make sense of classroom and everyday experiences that involve science (Fig. 2). Students need to articulate, represent, critique, apply, and extend their emerging understandings about science, using what they learn to make sense of new situations and solve new problems. For instance, Fig. 1 applies ideas about air developed in the classroom to a new situation that involves helium. The context (gas inside a balloon) is the same, encouraging students to generalize about gases in a balloon, whereas the text encourages them to generalize further about gases, regardless of the type of container. Instructional materials need to include tasks or question sequences that guide student interpretation and reasoning about experiences, data, and texts and that support them in considering how those ideas apply to phenomena not experienced in science class.

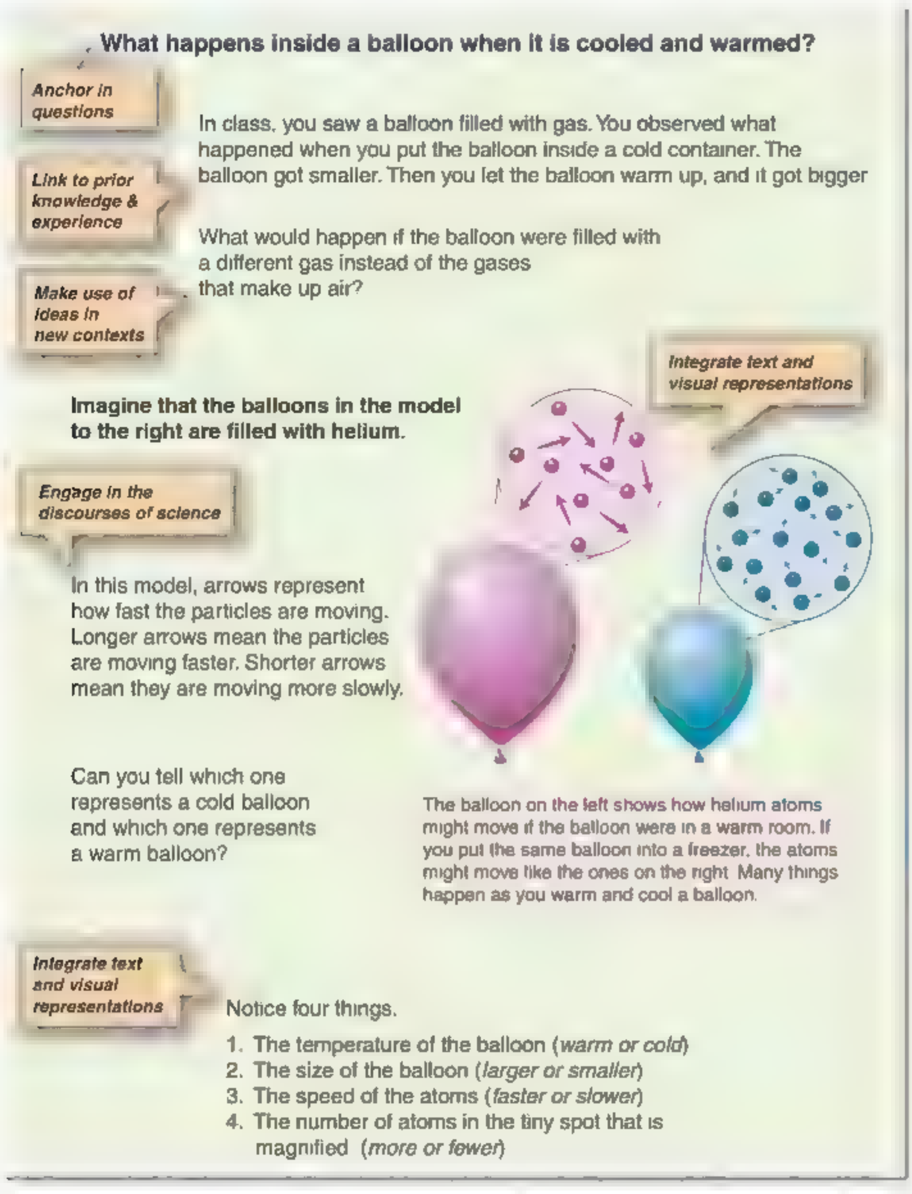
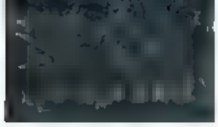


Fig. 1. Excerpt from a sixth-grade chemistry text connecting students' in-class experiences with a new example (*9*).

A fifth literacy practice essential to fostering inquiry in the classroom is engaging students in constructing explanations and arguments, which are essential components of scientific discourse. It is critical for students to have opportunities to talk and write about science and to practice supporting their ideas with evidence. Much work has been done in the area of writing and its many purposes in science, ranging from recording and organizing data to proposing written explanations and making arguments for why evidence supports one conclusion more than another. The latter, writing to explain or argue a position to an audience, is a critical aspect of engaging in inquiry. The discourse of science (*21*, *22*) includes not only precise language but also particular ways in which language is used, conclusions are drawn, ideas are put together, explanations are constructed, and arguments are presented. Each of these is of critical importance in engaging in science as a reader or writer of scientific ideas and also as a student and citizen.

Written and oral communication in the context of science inquiry depend on the use of data as evidence for explanation and argumentation. To explain phenomena, scientists require evidence to support their claims, and their explanations need to employ the language and ideas of science in ways that illustrate how they reasoned from available evidence (*23*). Materials and instruction can support students in writing scientific explanations by providing a framework for this practice: Make a claim, provide evidence, use reasoning that incorporates scientific principles to explicitly link the claim and evidence, and consider the validity of alternative explanations (*24*, *25*). In any science exposition (written or oral), students must pay attention to the evidence to support claims, the ways in which the evidence is used, and whether the evidence is sufficient and appropriate (that is, whether it supports the claim and is accurate) (*26*, *27*).

Scientific literacy for a global society in the 21st century is built on understanding science concepts and principles, as well as on



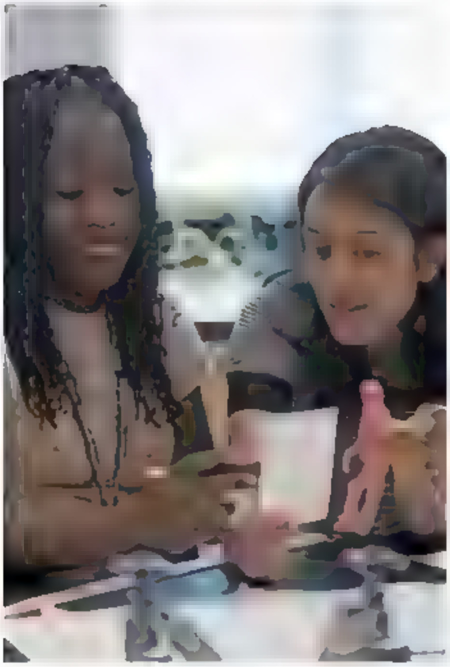


Fig. 2. A teacher helping a middle school student interpret text related to an in-class activity. [Photo credit: Mike Gould]

engaging in the literacy practices that make investigation, comprehension, and communication of ideas possible. Integration of literacy practices and inquiry-science education encourages instructional strategies that build on students' curiosities about the world and support students in building fundamental literacy skills. Although most students will not pursue careers in scientific fields, most will probably read science-related materials throughout their lives. For today's students to participate effectively in tomorrow's decision-making as consumers, members of the electorate, and members of society, it is imperative that educators support students in reading, writing, and communicating in science.

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REVIEW

Literacy and Science: Each in the Service of the Other

P. David Pearson,[1*] Elizabeth Moje,[2] Cynthia Greenleaf[3]

We use conceptual and empirical lenses to examine synergies between inquiry science and literacy teaching and learning of K-12 (kindergarten through high school) curriculum. We address two questions: (i) how can reading and writing be used as tools to support inquiry-based science, and (ii) how do reading and writing benefit when embedded in an inquiry-based science setting? After elaborating the theoretical and empirical support for integrated approaches, we discuss how to support their implementation in today's complicated curricular landscape.

Scientific literacy has been the rallying cry for science education reform for the past 20 years, yet this phrase has had multiple, and sometimes conflicting, meanings. Does it refer to the reading and writing of science texts? Is it about learning how to think and practice like a scientist? Or does it refer more generally to knowing science for everyday life? Is literacy an aspect of scientific inquiry? Equally important, why does scientific literacy matter?

The last question is, perhaps, easiest to answer. Development of a scientifically literate citizenry has been tied to the future of robust democratic society (*1*, *2*). Explicit calls for proficiency in reading and science literacy for all (*1*–*4*) envision a populace capable of fully participating in the workplace and civic demands of the 21st century. This demand for a scientifically literate populace, however, requires a clear definition of science literacy and how to develop it.

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A review of the literature reveals two dominant understandings of scientific literacy. One focuses on familiarity with the natural world and with key science concepts, principles, and ways of thinking (*2*). The other, which is the focus of this essay, makes explicit connections among the language of science, how science concepts are rendered in various text forms, and resulting science knowledge (*5*). Researchers guided by this latter view are concerned with how students develop the proficiencies needed to engage in science inquiry, including how to read, write, and reason with the language, texts, and dispositions of science. The ability to make meaning of oral and written language representations is central to robust science knowledge and full participation in public discourse about science (*6*, *7*).

However, text and reading can actually supplant science inquiry through text-centric curricula; these are the very curricula that science educators criticize when they champion hands-on, inquiry-based curricula (*8*, *9*). But when science literacy is conceptualized as a form of inquiry, reading and writing activities can be used to advance scientific inquiry, rather than substitute for it. When literacy activities are driven by inquiry, students

simultaneously learn how to read and write science texts and to do science (*5*, *6*, *10*).

Literate Practice as Inquiry

In many reform-oriented science classrooms in the United States, texts are deemphasized to avoid the common practice of reading about science in lieu of doing science (*2*, *8*, *9*, *11*, *12*). Yet scientists use reading and writing to inquire about scientific phenomena. No scientist simply walks into a lab and starts manipulating materials, tools, and phenomena. Investigations are always framed by other investigations. Texts are the artifacts of those past investigations and are used for inductive reasoning about scientific phenomena. Scientists use texts to generate new research questions and to provide the background necessary for research design and investigation.

"...the sense-making tools of science are consistent with, if not identical to, those of literacy..."

Science literacy instruction should engage children and youth in making sense of scientific texts as one form of scientific inquiry. Inquiry-driven literate practice is not simply passive receipt of information about science but rather a process of actively making meaning of science; these inquiries are best regarded as investigations in their own right. When reading and writing are cast as tools for investigating phenomena, students can learn how to build on and expand the work of other scientists by reading about the designs and findings of others (*10*). We can also engage students in producing texts that represent the ways they make sense of investigations, thus helping students understand how and why scientists think, write, and shape arguments the way they do. For example, in one project with middle- and high-school youth (*13*, *14*), teachers regularly ask students to evaluate whether their written claims refer back to the hypotheses they made, whether they made the data evident, and whether they have provided reasoning for their claims. Students can also learn to use writing in the way that scientists do for both journaling (*15*) and public reporting (*13*, *16*). In short, literacy has a role to play in both first-hand (hands-on) and secondhand (text-based) investigations (*15*).

Careful comparisons of the reasoning tasks required of K-12 (kindergarten through high school) students when they engage in hands-on and text-based inquiries reveal a number of shared processes and skills (*9*, *17*, *18*). Science and literacy use many of the same reasoning processes: setting purposes, asking questions, clarifying ambiguities, drawing inferences from incomplete evidence, and making evidence-based arguments (*10*, *19*, *20*).

Science as a Setting for Enhancing Literacy

Just as literacy tools and artifacts can enhance the acquisition of knowledge and inquiry in science, so too can science provide an ideal context for acquiring and refining literacy tools. Several scholars (*7*, *21*–*23*) have argued that without systematic attention to reading and writing within subjects like science and history, students will leave schools with an impoverished sense of what it means to use the tools of literacy for learning or even to reason within various disciplines. Science provides a setting in which students are intellectually obligated to make sense of data, draw inferences, construct arguments based on evidence, infer word meanings, and, of course, construct meanings for text—the very dispositions required as good readers and writers. Students fine-tune their literacy tools not only when they read and write science texts but also when they engage in science investigations precisely because so many of the sense-making tools of science are consistent with, if not identical to, those of literacy (*24*), thus allowing a setting for additional practice and refinement that can enhance future reading and writing efforts.

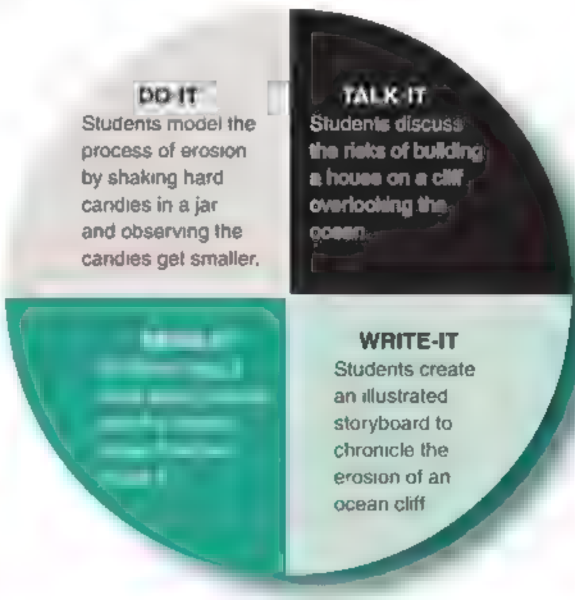


Fig. 1. A multimodal approach to learning about the concept of erosion. Reprinted from (*60*). [Copyright 2010 by The Regents of the University of California]

Challenges to Science Literacy Instruction

With all of these reasons for valuing science literacy instruction, one might wonder why such practice is not de rigueur? And given that it is not, what needs to be done to make it possible for young people to regularly read and write texts as an aspect of scientific inquiry?

A number of current realities prevent teachers from engaging in integrated science literacy instruction. One is the view of text held by many science educators described earlier—that our text-centric focus has overshadowed science inquiry (*9*, *12*, *25*). Both science and literacy educators agree that text-only science is weak science instruction, but most recognize that doing science involves reading and writing print and other symbol systems and graphic representations (*7*, *26*). Scientists cannot conduct scientific investigations or represent their findings without text-based inquiry tools (*10*, *14*).

A second challenge is the poor quality of texts available for science instruction. Typical science textbooks are dense and disengaging to inexperienced science readers (*9*, *11*, *22*, *27*). Science teachers have little access to well-designed texts that readers can understand given their developing knowledge base and varying reading skill levels (*27*).

This leads to a third challenge: Both teachers and students could be better at reading, writing, teaching, and learning from science texts. Students struggle with the abstract concepts, with a challenging scientific lexicon and set of discourses, and with complex images, graphs, and charts (*22*, *28*, *29*). Teachers, for their part, are often not well educated in science (at the elementary level) or in scientific-specific modes of literacy instruction (at the secondary level).

When reading is not conceptualized as inquiry, texts are complex, students' reading skills are weak, and teacher knowledge is uncertain, teachers often resort to telling students about science rather than actively engaging students in making sense of it (*30*, *31*). Likewise, when high-stakes testing drives teachers to cover content rather than actively engage students in the learning process, lectures offer an efficient form of delivering science information; thus, reading about science is replaced by listening to someone talk about science (*25*, *32*). Avoiding the challenge of engaging students with texts may seem efficient, yet it ultimately undermines student learning. Instead of confronting reading problems head on, it breeds student dependence on the teacher for science knowledge and places the learner in a passive role (*33*, *31*). At the same time, simply making texts available in print or online is not enough to ensure that students engage with them, rather, students need explicit support

to acquire the composing and comprehension processes needed for successful reading and writing in science (*34–36*).

Other major challenges to developing scientific literacy in the United States are the accountability systems that schools and statehouses are beholden to in today's policy environment. First, at the elementary school level, thanks largely to the zeal with which the No Child Left Behind (NCLB) initiative promoted reading and math over science and other subjects, there is precious little time for science (*37*). A 2008 national survey revealed that a majority of elementary schools decreased the time allotted to science by 15 minutes per day, while time for reading and math was increased by a like amount (*37*). A 2008 survey of elementary schools in the San Francisco Bay Area (*38*) revealed an even more alarming reduction in time devoted to science in the wake of NCLB—to under 60 minutes per week (in comparison to a national average of 200 minutes per week in 2001). Second, standardized multiple-choice tests for all subjects serve as the standard for gauging student achievement in modern accountability systems (*39*). As a consequence, schools are hard pressed to promote inquiry-based teaching, irrespective of whether it is grounded in laboratory experiences or text-based investigations, in the face of tests that privilege the assessment of facts over concepts or knowledge frameworks. The combination of high stakes (rewards and sanctions based on performance) and low intellectual challenge (the factual character of the vast majority of test items) almost compels teachers to eschew deep inquiry in favor of content coverage (*31*).

> "Science learning entails and benefits from embedded literacy activities. . . literacy learning entails and benefits from being embedded within science inquiry."

The Evidence Base for Integrated Science Literacy Initiatives

These realities represent daunting challenges to promoting integrated science literacy instruction. However, promising projects at various grade levels employ literacy tools, including text, to support rather than supplant the acquisition of knowledge and inquiry in science. These efforts share key ingredients: They are embedded in inquiry-based science instruction; they engage learners in text-based inquiries along with hands-on science investigations; they bring together teams of literacy and science experts; and they require extensive teacher learning through professional development and/or educative curriculum materials (*40, 41*). In this section, we provide brief descriptions of some promising science literacy research and development projects. They move both science and literacy instruction toward a more authentic expression of the nature of science. Most important, these efforts show promise of increasing student learning in both literacy and science.

Concept-Oriented Reading Instruction (CORI). For nearly 20 years, Guthrie and colleagues have been refining CORI, a program designed to promote a number of literacy goals through the use of broad interdisciplinary themes (*42*), primarily drawn from science curricula, such as exploring the impact of humans on animal habitats. CORI provides explicit instruction in reading strategies, such as questioning, activating background knowledge, searching for information, summarizing, and synthesizing information in order to communicate with others. Instruction involves hands-on investigations, inquiry with text, strategy instruction, working in collaborative inquiry teams, and writing to publish and present findings. CORI has been shown to increase students' science concept learning, motivation, use of productive inquiry strategies, and overall text comprehension compared to control classrooms with separate science and literacy curricula and/or strategy instruction in reading alone (*43*). Of particular interest in the CORI research is the pivotal role that motivation, in all of its instantiations (interest, self-efficacy, and achievement motivation), plays in learning both science and literacy.

Guided Inquiry supporting Multiple Literacies (GIsML). Palincsar and Magnusson (*15*) engaged in a multiyear program of research on the ways that text-based (secondhand) inquiry investigations can support students' conceptual understanding in hands-on (firsthand) investigations. In GIsML professional development, teachers learn to engage students in cycles of investigation guided by specific questions, establishing the classroom as a community of inquiry. GIsML combines these firsthand and secondhand experiences through the use of a fictional working scientist's notebook. The notebook provides models of data representation and engages students in interpreting data along with the scientist. The texts also model a scientist using secondhand materials, reading and interpreting with a critical stance, and drawing conclusions from multiple sources of evidence. After students investigate scientific questions, they consult text to learn how the scientist has interpreted similar evidence. In a quasi-experiment comparing fourth graders studying the concept of light by working with either a GIsML notebook or a considerate text (i.e., especially well-written, cohesive expository text) treatment, they found that students learned more in the GIsML notebook-based instruction than in the considerate text condition, concluding that the notebooks promoted talk that led to greater engagement and, ultimately, improved understanding (*15*).

In-depth Expanded Applications of Science (Science IDEAS). Romance and Vitale (*44, 45*) developed the IDEAS model of integrated science/language instruction, which replaces the time allocated for traditional literacy instruction with a 2-hour block of science that includes literacy skills. The science instruction is concept-focused and involves firsthand experiences, attention to science process skills, discussion, reading comprehension, concept mapping, and journal writing. Several multiyear efforts show that Science IDEAS students outperform students receiving segregated language arts and science instruction on a range of reading and science tests and indices of self-efficacy and attitudes toward science (*44–46*).

Seeds of Science—Roots of Reading. Seeds and Roots (*10*) began as an attempt to embed inquiry-oriented reading, writing, and language activities within the already successful GEMS (Great Explorations in Math and Science) K-8 hands-on science program. The program is based on the fundamental principle that literacy is best enacted as a set of learning tools that support knowledge acquisition rather than as a set of independent curriculum goals. Across two external evaluations comparing Seeds and Roots with content-controlled inquiry science (and, in one instance, a reading-only control), this experimental curriculum shows advantages on measures of science learning, vocabulary acquisition, and writing fluency, with a less consistent advantage for reading comprehension (*47, 48*). (See Fig. 1 for an example.)

Reading Apprenticeship. Greenleaf and colleagues have been developing discipline-based literacy instruction and professional development (under the rubric of Reading Apprenticeship) to foster more engaged learning for underprepared students in secondary and post-secondary settings (*19*). In this apprenticeship model, science teachers inquire deeply into what they do to derive meaning with complex science texts, including explanation and exposition in scholarly journals, as well as the diagrams, data arrays, mathematical expressions, and graphs that convey information. Teachers then learn classroom routines for engaging students in active inquiry and sense-making with such texts, routines for mentoring students in productive reasoning processes, for fostering metacognitive awareness of comprehension problems and problem-solving processes, and for promoting collaborative discussions of science texts. A randomized experiment of high-school

biology teaching and learning demonstrated that the program significantly improved the quality of biology and literacy integration and resulted in statistically significant improvements on state standardized tests in English language arts, reading comprehension, and biology for students (*49*).

Textual tools. In work of Moje and her colleagues with middle- and high-school youth in Detroit (*14*, *50*, *51*), teachers engage students in reading both scientific and lay-audience texts related to the phenomena under study. The teachers also engage students in translating across multiple forms of representation (e.g., as investigations require data to be logged and explanations of phenomena to be communicated). Students engage in peer review to evaluate whether their written explanations refer back to the hypotheses they made, to what extent they made the data evident, and the quality of reasoning they have provided for their claims. Students across all classrooms—regardless of entering skill level—demonstrated more developed, scientifically accurate, and rhetorically appropriate (to science) explanations when compared to their writing at the outset of the interventions, as well as significant gains in science concept knowledge (*14*).

"...schools are hard pressed to promote inquiry-based teaching... in the face of tests that privilege the assessment of facts over concepts or knowledge frameworks."

Summary and critique. This body of evidence [see also (*34*, *52*–*54*)] demonstrates the promise of integrated approaches to literacy and science instruction. At a time when struggling students are likely to be taken out of their science classes to attend remedial reading classes, these findings suggest that a better option may be to attend to the needs of struggling readers within science class, where they simultaneously acquire subject-matter knowledge and inquiry skills, and perhaps even improve their literacy skills. But the promise we see must be tempered by the fact that this line of work is relatively young, and much needs to be learned about which of the features commonly employed in these designs are truly the active ingredients responsible for student learning and which are more peripheral.

Moving Forward

Greater proficiency in science reading, writing, and inquiry for all students requires knowledgeable teachers who understand the vital role literacy plays in enhancing rather than replacing science learning and who can mentor their students in these practices. Teacher knowledge is the key to advancing student achievement. However, many institutional barriers stand in the way. First, the structure of teacher education virtually guarantees isolation between literacy and science preparation. Moreover, the default practice of giving science teachers a literacy strategies toolkit is not likely to promote deep thinking and reasoning around texts and investigations that support science learning (*50*). Instead, teaching literacy in scientifically specific ways requires deep conceptual change for teachers to help them adopt new ways of thinking and acting in the classroom. Changes of this magnitude will require rethinking teacher preparation, professional development, and curriculum.

Initial teacher preparation. Moje and colleagues (*55*) have redesigned the secondary teacher education program at the University of Michigan to focus on building understanding of the disciplinary practices supported by reading, writing, and reasoning, rather than treating literacy methods as a separate subject. Donahue (*56*) and Braunger, with other teacher educators (*57*), have designed similar discipline-centered approaches for secondary teachers. These models offer the opportunity for preservice teachers to examine the texts of science, to plan instruction that integrates complex uses of text into inquiry, and to learn how to teach young people how to think, read, and write like scientists.

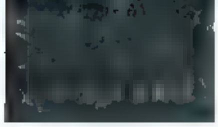
Ongoing professional development. Many science teachers hold misconceptions, or at the very least, limited conceptions, of literacy teaching and learning; they tend to think of reading and writing as basic and universal skills that are developed in elementary or middle school or down the hall in the English department. They do not expect to teach science reading and writing to students, yet they are confronted with students who do not comprehend science texts, their specialized language, or the many ways science ideas are conveyed through print, diagrams, images, models, graphs, and tables. Greenleaf and colleagues (*58*) have developed programs designed to challenge teachers' misconceptions, transforming them into more robust conceptions of science reading and its role in learning. Confronting teachers with highly advanced texts that place them in a struggling position (not unlike the texts their secondary students confront daily) helps them realize that reading is neither automatic nor straightforward. They typically emerge with a new appreciation for the challenges their students face and insights about how they can help students cope with those challenges. These science teachers also begin to recognize how poorly many of our textbooks represent authentic reading and writing about science (*23*) and how difficult it would be for their English language arts colleagues to assume responsibility for mentoring and engaging students in the rigors and rewards of science reading. Such opportunities to investigate science literacy practices need to be made available to teachers on a broad scale.

Curriculum development. Over the past 30 years, many inspired efforts to fundamentally reform the K-12 science curriculum have been launched to engage students in investigation and inquiry; however, the quality of science reading materials and the role they play in inquiry have often been overlooked in these efforts. A new generation of materials takes a different approach, assuming that science learning entails and benefits from embedded literacy activities and that literacy learning entails and benefits from being embedded within science inquiry. Further, some new curricula provide resources to learn needed science content, literacy practices, and pedagogies that support student learning (*59*). Those involved in creating and validating the efficacy of these new programs should press educational publishers to consider their approaches as viable alternatives to the status quo.

Assessment. Finally, it is important to note that all the professional development in the world will have little impact if we cannot also create more balanced assessment portfolios for our accountability systems (*39*). The inclusion of challenging performance tasks—tasks that involve extended inquiry (over several days), analysis of findings, and public reports of student work—would help to promote the very sort of inquiry that research documents as effective. However, as long as low-challenge, multiple-choice tests serve as the primary metric for measuring student learning and teacher quality, not only in science but in literacy as well, it will be difficult for teachers to take the risk of promoting genuine inquiry in their classes.

Inquiry As the Common Core

As a final point, we emphasize that all of our suggestions for moving ahead are really suggestions for making inquiry the common theme of reform. Teacher learning is most profound when teachers can employ the very same inquiry processes for their own professional learning that they aspire to enact with their students. By making their own learning about literacy and science pedagogy the object of inquiry, teachers can simultaneously develop the insights and pedagogical strategies they will need to mentor their students. Integrated curricula of the sort supported by empirical research require that the dispositions and practices of inquiry-based science be appropriated for inquiry in reading and writing. And finally, we must reshape our assessment systems to better reflect the nature and goals of inquiry-oriented instruction in both science and literacy. If we can manage all



of these initiatives, we might be able to help teachers situate literacy and science each in the service of the other as students gain tools and proficiency in both. The agenda is surely daunting, but the costs of avoiding it are high and the rewards for pursuing it are substantial

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REVIEW

Arguing to Learn in Science: The Role of Collaborative, Critical Discourse

Jonathan Osborne

Argument and debate are common in science, yet they are virtually absent from science education. Recent research shows, however, that opportunities for students to engage in collaborative discourse and argumentation offer a means of enhancing student conceptual understanding and students' skills and capabilities with scientific reasoning. As one of the hallmarks of the scientist is critical, rational skepticism, the lack of opportunities to develop the ability to reason and argue scientifically would appear to be a significant weakness in contemporary educational practice. In short, knowing what is wrong matters as much as knowing what is right. This paper presents a summary of the main features of this body of research and discusses its implications for the teaching and learning of science.

The goal of science is to produce new knowledge of the natural world. Two practices essential to achieving this objective are argument and critique. Whether it is new theories, novel ways of collecting data, or fresh interpretations of old data, argumentation

is the means that scientists use to make their case for new ideas. In response, other scientists attempt to identify weaknesses and limitations; this process happens informally in laboratory meetings and symposia and formally in peer review (*1*, *2*). Over time, ideas that survive critical examination attain consensual acceptance within the community, and by discourse and argument, science maintains its objectivity (*3*). Critique is not, therefore, some peripheral feature of science, but rather it is core to its practice, and without argument and evaluation, the construction of reliable knowledge would be impossible. Whether it is the theoretician who is developing new models of phenomena or the experimentalist who is proposing new ways of collecting data, all scientists must subject their ideas to the scrutiny of their peers. But what of science education?

Science Education and the Absence of Argument

Science education, in contrast, is notable for the absence of argument (*4*, *5*). Although instructors and teachers may offer many explanations, these are not arguments. To offer an explanation of a fact is to presume it is true. An argument, in contrast, is an attempt to establish truth and commonly consists of a claim that may be supported by either data, warrants (that relate the data to the claim), backings (the premises of the warrant), or qualifiers (the limits of the claim) (Fig. 1). Some or all of these elements may be the subject of rebuttals or counter-arguments (*6*). Arguments containing rebuttals are thought to be of the highest quality, as they require the ability to compare, contrast and distinguish different lines of reasoning. Within science, arguments may be verbal or written and are commonly reliant on supporting visualizations in the form of graphs or symbolic models.

Typically, in the rush to present the major features of the scientific landscape, most of the arguments required to achieve such knowledge are excised. Consequently, science can appear to its students as a monolith of facts, an authoritative discourse where the discursive exploration of ideas, their implications, and their importance is absent (*7*). Students then emerge with naive ideas or misconceptions about the nature of science itself—a state of affairs that exists even though the National Research Council; the American Association for the Advancement of Science; and a large body of research, major aspects of which are presented here, all emphasize the value of argumentation for learning science (*8*–*10*).

The common explanation of the absence of argument is that it is a product of an overemphasis by teachers, curricula, and textbooks on what we know at the expense of how we know (*11*). Deep within our cultural fabric, education is still seen simplistically as a process of transmission where knowledge is presented as a set of unequivocal and uncontested facts and transferred from expert to novice. In this world-view, failure of communication is the exception and success the norm. However, in reality, education is a highly complex act where failure is the norm and success the exception (*12*). For instance, a meta-analysis of 14 classes taught using traditional methods shows that students achieved an average gain of only 25% between their pre- and posttest scores. In contrast, when lecturers paused and asked students to discuss the concept presented in pairs or small groups (three or four students), students achieved an average gain of 48% (*13*).

Argumentation and Learning Science

Over the past two decades, in an attempt to address the problem posed by the failure of traditional methods, educational research has explored the contribution of collaborative discourse and argumentation to learning. Drawing on theoretical perspectives that see language as core to learning and thought and language as inseparable, the implications of these ideas for education have been developed by a number of theorists (*14*–*17*). A critical feature of this work is a view that learning is often the product of the difference between the intuitive or old models we hold and new ideas we encounter (*18*). Through a cognitive process of comparison and contrast, supported by dialogue, the individual then develops new understanding. Consequently, learning requires opportunities for students to advance claims, to justify the ideas they hold, and to be challenged. Although this may happen within the individual, it is debate and discussion with others that are most likely to enable new meanings to be tested by rebuttals or counter-arguments.

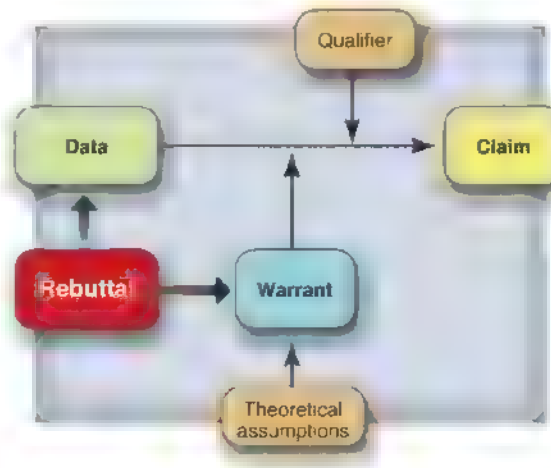

Fig. 1. Toulmin's argument diagram offers a generic representation of all arguments that are claims to knowledge (*6*). For instance, the claim that climate change is happening is supported by data, e.g., rising CO_2 levels, melting glaciers. A warrant is the justification that explains the relation of the data to the claim. Often, warrants rest on theoretical assumptions that are only tacitly acknowledged. Finally, qualifiers express the limits of the validity of the claim. Arguments arise when attempts are made to rebut or refute the claim either by attacking the validity of the data or the validity of the warrant. In science, arguments arise over the predictions and validity of theories, the methods of collecting data, and the interpretation of data sets.

In this sense, learning to argue is seen as a core process both in learning to think and to construct new understandings (*19*, *20*). Comprehending why ideas are wrong matters as much as understanding why other ideas might be right. For example, students who read texts that explained why common misconceptions were flawed (as well as explaining why the right idea was right) had a more secure knowledge than those who had only read texts that explained the correct idea (*21*). Likewise, researchers have found that groups holding differing ideas learn more than those who hold similar preconceptions, many of whom made no progress whatsoever (*22*, *23*). Indeed, one study found that even if the difference between individuals was based on incorrect premises, significant learning gains can occur—a case of two wrongs making a right—and with learning effects that were still significant on delayed posttests (*24*).

These findings are also supported by a number of classroom-based studies, all of which show improvements in conceptual learning when students engage in argumentation (*25*–*28*) (Fig. 2). For instance, students who were asked to engage in small-group discussions significantly outperformed a group of control students in their use of extended utterances and verbal reasoning (*25*), features that are rare in formal science education (*29*). Significant improvements were also produced in their nonverbal reasoning and understanding of science concepts. Another study with two classes of 16- to 17-year-old students studying genetics required students to engage in argumentative discourse about the appropriate answer to specific problems. Compared with a control group, the students who engaged in discussion used biological knowledge appropriately (53.2 versus 8.9%) significantly more often (*26*).

A recent meta-analysis of 18 studies grouped learning activities into three major categories: those that are interactive and require collaborative discourse and argumentation (either with a peer or an expert tutor); those that are constructive and require individuals to produce a product

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such as an essay or lab report; or those that are active, such as conducting an experiment (30). Comparing the learning gains achieved when using each of these three approaches, the work shows conclusively that a hierarchical schema of learning activities exists from interactive (the most effective), to constructive, to active (the least effective). Studies show, however, that group discourse that contributes to learning effectively is dependent on a number of factors. Most important, students need to be taught the norms of social interaction and to understand that the function of their discussion is to persuade others of the validity of their arguments. Exemplary arguments need to be modeled, and instructors need to define a clear and specific outcome. Student groups need materials to support them in asking the appropriate questions and to help in identifying relevant and irrelevant evidence; also, consideration needs to be given to the relative ability of group members (31–34).

Fig. 2. Scientists routinely debate their theories, their data, and the implications. Research shows that argumentation in the classroom can improve conceptual learning.

Scientific Reasoning and Argumentation

Argumentation in science education requires students to construct and evaluate scientific arguments and to reason scientifically. The picture that research presents of students' ability to undertake scientific reasoning is complex (35). Students' ability to argue would appear to depend on the nature of the possible outcome, with students tending to adopt reasoning strategies with a confirmatory bias rather than using logical criteria. It is also dependent on their domain-specific knowledge. For instance, individual's ability to identify covariation is significantly enhanced by knowledge of a plausible theoretical mechanism (36), for example, that levels of carbon dioxide in the atmosphere could be a cause of climate change. The situation is somewhat confounded, however, by a recent study where Chinese physics undergraduates outperformed comparable American undergraduates on tests of content knowledge, in some cases by three effect sizes, yet there was no difference in their performance on a domain-general test of scientific reasoning (37). Moreover, there is disagreement about how and when students capabilities with reasoning develops between those who argue that it develops through adolescence versus those who argue that even preadolescent children are capable of making evidence-based inferences (38)—essentially that the limits on student's capability is attributable to their lack of knowledge rather than their reasoning capability.

In addition, notions of what constitutes scientific reasoning differ somewhat. Much of the research on individual's capability with scientific reasoning is a product of laboratory-based, psychological research examining individuals skills with specific competencies. Early Piagetian studies defined scientific reasoning as the capability to undertake a set of logico-mathematical operations such as seriation, logical reasoning, probabilistic thinking, and manipulating abstract variables—for instance, whether students could conserve volume when water was transferred from a thin, tall cylinder to a wide, short, one (39). More recent research has focused on a wider set of skills such as students' ability to develop testable hypotheses, to generate experimental designs, to control variables, to coordinate theory and evidence, and to respond to anomalous evidence (35).

"Critique is not, therefore, some peripheral feature of science, but rather it is core to its practice, and without [it], the construction of reliable knowledge would be impossible."

Sociologists, however, offer a different, empirically based vision of scientists marshalling resources to mount persuasive arguments for the validity of their cases. Philosophers, in contrast, offer a normative, idealized description of how science functions. A synthesis of the work from these three domains would suggest that the reasoning skills that science education might seek to develop are these abilities:

- to identify patterns in data, such as covariation, and to make inferences;
- to coordinate theory with evidence and to discriminate between evidence that supports (inclusive) or does not support (exclusive) or that is simply indeterminate;
- to construct evidence-based, explanatory hypotheses or models of scientific phenomena and persuasive arguments that justify their validity; and
- to resolve uncertainty, which requires a body of knowledge about concepts of evidence such as the role of statistical techniques, the measurement of error, and the appropriate use of experimental designs, such as randomized double-blind trials.

The study of reasoning also offers an opportunity to explore the types of arguments used in science, which may be abductive (inferences to the best possible explanation), such as Darwin's arguments for the theory of evolution; hypothetico-deductive, such as Pasteur's predictions about the outcome of the first test of his anthrax vaccine; or simply inductive generalizations archetypal represented by "laws."

Enhancing Student Argumentation and Reasoning Skills?

Do students become better at scientific reasoning if it is an overt feature of their education? Many studies have shown that explicit teach-

ing of specific strategies does improve students' scientific reasoning. For instance, a laboratory-based study found that the performance of students explicitly taught about the control of variables through a structured intervention improved significantly compared with a group who were given no such instruction (*40*). Similar findings emerge from a recent classroom-based study that showed significant developments in students' strategic and meta-strategic thinking (*41*). The strongest evidence comes from a U.K. classroom-based study using 30 lessons dedicated to the teaching of reasoning over 2 years in 11 schools with children from grades 7 and 8. Students' scores on test of conceptual knowledge in the intervention schools were significantly better than those of the control sample (*42*). Additionally, 2 years later, these students significantly outperformed a control sample not only in science, but also in language arts and mathematics, which led the authors to argue that their program had accelerated students' general intellectual processing abilities. This finding has been replicated many times by the same authors, who have collected data from new cohorts in the schools that use this program. The form of reasoning measured here, however, was restricted to the students' ability to perform logical operations based on Piaget's studies. In a 1-year classroom intervention aimed at improving students' ability to construct arguments, they showed improvements, but these were not significant (*43*).

Future Challenges

Research on the development of students' skills in argumentation is still in its infancy and lacking valid or reliable instruments with which students' competency can readily be assessed. In addition, we still need to understand in greater detail how argumentation produces learning and what features of learning environments produce the best arguments among students (*44*). Much is understood about how to organize groups for learning and how the norms of social interaction can be supported and taught, but how such groups can be supported to produce elaborated, critical discourse is less evident (*45*). Where studies are unequivocal, however, is that if student skills are to develop not only must there be explicit teaching of how to reason but also students need a knowledge of the meta-linguistic features of argumentation (claims, reasons, evidence, and counterargument) to identify the essential elements of their own and others' arguments (*46*). Younger students, particularly, need to be desensitized to the negative connotation of conflict surrounding these words and to see argument as a fundamental process in constructing knowledge.

What is in little doubt is that employers, policy-makers, and educators believe that individuals' ability to undertake critical, collaborative argumentation is an essential skill required by future societies (*47*). Of its own, the evidence from research to date is that mere contact with science does not develop such attributes. Indeed, the cultivation of critical skepticism, a feature that is one of the hallmarks of the scientist, would appear to have only minimal value within science education. Yet, research has demonstrated that teaching students to reason, argue, and think critically will enhance students' conceptual learning. This will only happen, however, if students are provided structured opportunities to engage in deliberative exploration of ideas, evidence, and argument—in short, how we know what we know, why it matters, and how it came to be. Evidence would also suggest that such approaches are more engaging for students (*48*). Collaborative discourse where students engage constructively with each other's ideas therefore offers a means for improving the quality of the student experience, the depth of student thinking, and their learning of science itself.

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Genotype to Phenotype: A Complex Problem

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Rapid genome-sequencing methods coupled with whole-genome transcription profiling suggests that it may be possible to predict phenotype from a genotype. Human genetic association studies of common single-nucleotide polymorphisms (SNPs) explain only a fraction of phenotypic variation among individuals (*1*). This may be due to rare SNPs (*1*), structural (*2*) and epigenetic variants, or multiple alleles with additive effects or synergistic genetic interactions associated with complex combinations of genetic variation (*3*).

To address the genotype-to-phenotype problem, we developed a simple comparative model for the budding yeast *Saccharomyces cerevisiae* that enables a comprehensive assessment of the genetic mechanisms leading to different phenotypes for the same mutation in two different genetic backgrounds. The strain Σ1278b mates and forms viable meiotic progeny with the reference strain, S288c, and the divergence between the two strains is roughly equal to the divergence between the genomes of two humans (*4*, *5*).

We sequenced and assembled the 12-Mb Σ1278b genome, annotating 6923 open reading frames (ORFs) and RNAs, of which 6848 have orthologs within S288c (*5*). The order of genes between the strains was the same (except in the highly variable subtelomeric regions), and the sequence of 46% of the Σ1278b ORFs was identical to those in S288c. Differences between the strains were largely due to small insertions and deletions or SNPs, with an average SNP density of 3.2 per kilobase.

We deleted ~5100 genes within Σ1278b (*5*) to systematically compare identical deletion mutants (*6*). In particular, we identified "conditional essentials," those genes required uniquely for viability in either strain (fig. S3 and table S1). We scored colonies as dead or alive and surveyed all vital pathways for individual-specific genetic interactions. We expected such conditional essential genes to be rare because the genomes of Σ1278b and S288c are nearly identical.

Although 894 genes were essential in both S288c and Σ1278b, 44 genes were essential only in Σ1278b and 13 genes were essential only in S288c (Fig. 1A). The conditional subsets included genes of various functions; however, the Σ1278b subset was enriched for genes involved in mRNA metabolic process, whereas the S288c set was enriched for genes annotated to SRP-dependent cotranslational targeting. These biological biases suggest that these phenotypes result from genetic interactions associated with an individual genotype.

Hybrid strain crosses and tetrad analysis focusing on 18 mutants that were lethal in Σ1278b with wild-type levels of fitness when deleted in S288c were used to investigate conditional essentiality. We mated viable haploid S288c deletion mutants to wild-type Σ1278b and analyzed the hybrid diploid progeny by tetrad analysis. The number of viable meiotic progeny carrying the deletion allele is related to the number of unlinked background-specific modifiers (*5*) that contribute to the genetic interaction. In all 18 cases, the conditional phenotype was associated with numerous modifier genes that differ between strains. The simplest cases, *SKI7* and *BEM1*, are likely due to a genetic interaction with at least two or more modifiers, but all other cases were more complex (Fig. 1B). Thus, our analysis showed that conditional essentiality is almost always a consequence of complex genetic interactions involving multiple modifiers associated with strain-specific genetic variation rather than classic digenic synthetic lethality (*6*, *7*).

Our genome-wide survey of conditionally essential genes demonstrates that in most cases a complex set of background-specific modifiers influence a mutation whose phenotype differs between individuals. These results raise the possibility that similar complex modifiers may largely explain the difficulty in identifying the genetic basis for individual phenotypes. The potential for genetic interactions to control individual phenotypes becomes even more important if different combinations of alleles can lead to the same physiological state. The ability to identify these conditional essential phenotypes in yeast provides a framework to unravel the fundamental principles of genetic networks resulting from natural variation, including those that underlie human disease.

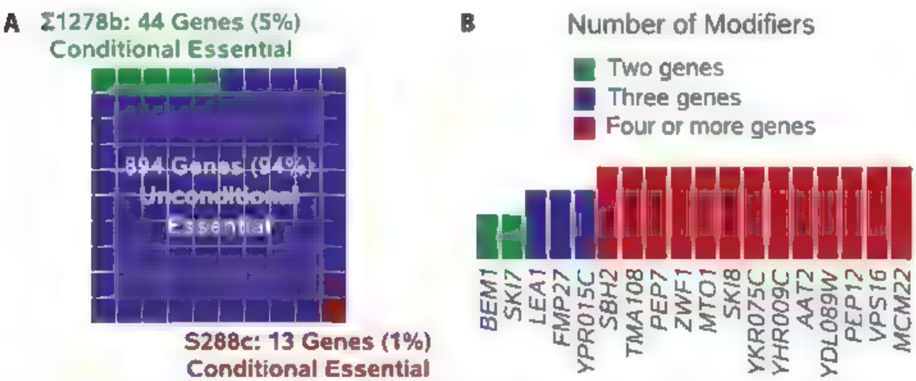

Fig. 1. **(A)** Most S288c essential genes are also essential in Σ1278b (94%); however, ~5% are essential only in the Σ1278b genetic background, whereas ~1% are essential only in S288c. **(B)** Conditional essential genes in Σ1278b are the consequence of complex genetics. χ^2 tests indicated the number of modifiers associated with conditional essentiality (*5*).

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Supporting Online Material

www.sciencemag.org/cgi/content/full/328/5977/469/DC1
Materials and Methods
Figs. S1 and S2
Tables S1 to S3
References

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Molecular Basis of Alternating Access Membrane Transport by the Sodium-Hydantoin Transporter Mhp1

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The structure of the sodium-benzylhydantoin transport protein Mhp1 from *Microbacterium liquefaciens* comprises a five-helix inverted repeat, which is widespread among secondary transporters. Here, we report the crystal structure of an inward-facing conformation of Mhp1 at 3.8 angstroms resolution, complementing its previously described structures in outward-facing and occluded states. From analyses of the three structures and molecular dynamics simulations, we propose a mechanism for the transport cycle in Mhp1. Switching from the outward- to the inward-facing state, to effect the inward release of sodium and benzylhydantoin, is primarily achieved by a rigid body movement of transmembrane helices 3, 4, 8, and 9 relative to the rest of the protein. This forms the basis of an alternating access mechanism applicable to many transporters of this emerging superfamily.

Secondary-active transporters effect the cellular uptake and release of a wide range of substances across biological membranes in all organisms. They do this by coupling the uphill movement of the substrate against its concentration gradient with the energetically favorable downhill gradient of a second substrate, often a proton or a cation (*1*, *2*). The kinetics and thermodynamics of these transporters can be explained by the alternating access model, for example (*3*–*6*), but the structural details of the necessary conformational changes are only partly understood.

Recently the structures have been reported of a number of transporters of different families that have the same fold as LeuT (*7*), a bacterial homolog of the mammalian serotonin neurotransmitter transporter. These include the sodium-galactose symporter vSGLT (*8*), the sodium-benzylhydantoin transporter Mhp1 (*9*), the sodium-betaine symporter BetP (*10*), and two amino acid transporters, AdiC (*11*, *12*) and ApcT (*13*). Dysfunction of members of this growing superfamily in humans can lead to diseases, including neurological (*14*) and kidney (*15*) disorders. Other members are implicated in cancer because they can supply tumor cells with nutrients (*16*), cause drug resistance (*17*), and/or provide a means of treatment (*18*).

The fold shared by these transporters is an "inverted repeat" motif with two sets of five transmembrane helices (TMs) oppositely oriented with respect to the membrane (*19*, *20*) (Fig. 1). The conformations observed for these transporters can be categorized into the following three classes: outward-facing, as observed in LeuT (*7*), Mhp1 (*9*), and AdiC (*11*, *12*); occluded, where a trapped substrate is blocked from exiting on either side of the protein, as seen in Mhp1 (*9*), BetP (*10*), and AdiC (*21*); and inward-facing, as in vSGLT (*8*) and ApcT (*13*). The alternating access model built up from these three conformations is accepted as a general concept for the LeuT superfamily of transporters (*19*, *20*). However, the details of the transport mechanism remain largely controversial because the model has been derived by comparing transporters with divergent amino acid sequences that transport a wide variety of substrates.

Here, we present the substrate-free inward-facing structure of Mhp1, a sodium-hydantoin transporter from *Microbacterium liquefaciens* (*9*, *22*, *23*) at 3.8 Å resolution (Fig. 1). By comparing this with our previous structures of the outward-facing

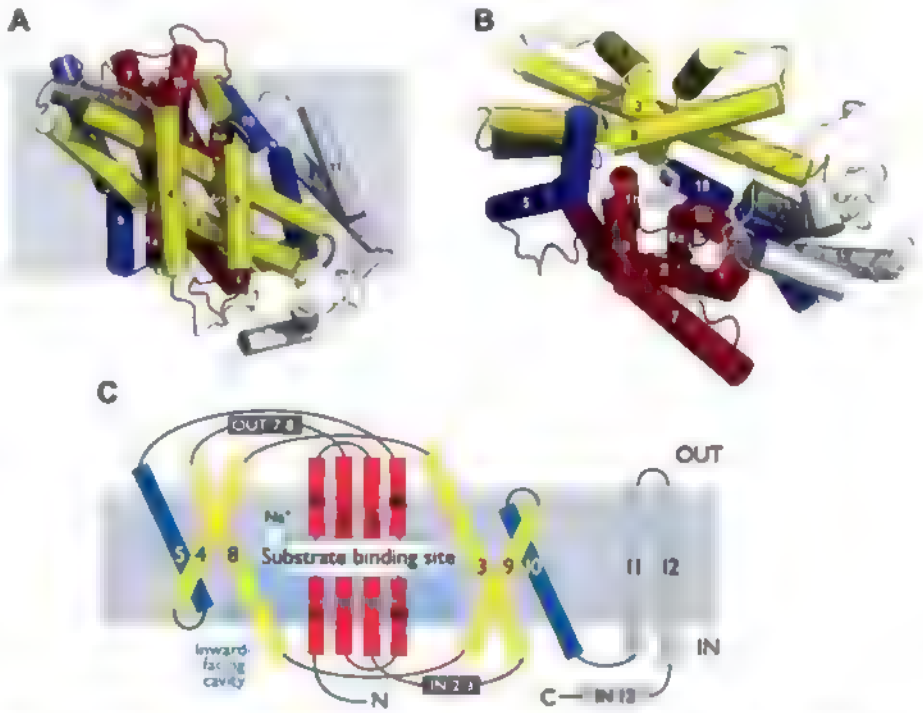

Fig. 1. Structure of the substrate-free inward-facing conformation of Mhp1. **(A)** Cartoon representation as seen from a viewpoint along the membrane. Each of the longer helices (TMs 5, 8–10) that show a distinct curvature is shown as two shorter helices broken in the middle. The cartoon has been colored with the bundle (TMs 1, 2, 6, and 7) in red, the hash motif (TMs 3, 4, 8, and 9) in yellow, the flexible helices (TMs 5 and 10) in blue, the C-terminal helices in light gray, and the small extracellular and cytoplasmic surface helices (IN 2-3, OUT 7-8) in darker gray. **(B)** As in (A), but viewed from the inside of the cell. To orient the reader, the positions of the sodium and benzylhydantoin that are observed in the occluded structure (*9*) are represented by a light gray sphere and sticks, respectively. **(C)** Topology diagram colored as in (A), illustrating the pseudo two-fold repeat unit.

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and occluded states (9) and using molecular dynamics simulations, the transition from the outward-facing to the inward-facing conformations is seen primarily as a simple relative rotation of two rigid-body domains in combination with the bending of two TMs. This straightforward mechanism synchronizes the opening and closing of the multiple "gates" in the Mhp1 molecule to implement the flow of substrate and ions.

Overall structure. The substrate-free inward-facing structure of Mhp1 was solved by the selenomethionine single-wavelength anomalous dispersion method and modeled using the high-resolution structure of the outward-facing conformation as a reference (9). Details are in the supporting online material (24). It was refined at a resolution of 3.8 Å to an R-factor of 27.3% and a corresponding R-free of 31.3% (table S1) (25). Despite the relatively low resolution of the data, the protein from residues 6 to 470 is well defined (fig. S1A), enabling ready comparisons with the outward-facing and occluded structures of Mhp1 (9).

Mhp1 is composed of 12 TMs. The first 10 constitute the conserved motif in which TMs 1 to 5 are related to TMs 6 to 10 by a pseudo two-fold axis along the plane of the membrane (Fig. 1C). It is convenient to describe the structure as being made of two major parts. The first is a four-helix bundle comprising TMs 1 and 2 and their pseudo two-fold equivalents TMs 6 and 7 (residues 23 to 86 and residues 193 to 278, respectively). The second is another motif of four helices formed from TMs 3 and 4 and their pseudo two-fold equivalents, TMs 8 and 9 (residues 101 to 159 and 296 to 355, respectively). TMs 4 and 9 pack at 60° onto one surface of TMs 3 and 8, giving the appearance of the hash sign (#) when viewed from a point in the plane of the membrane (Fig. 1A). These two motifs will be referred to as the bundle and the hash motif. TM 5 and two short surface helices (IN 2-3, OUT 7-8) link the two motifs together, and TM 10 connects the hash motif with the two C-terminal TMs (Fig. 1C). We have named TM 5 and TM 10 the "flexible helices" because they bend during the state transitions described below.

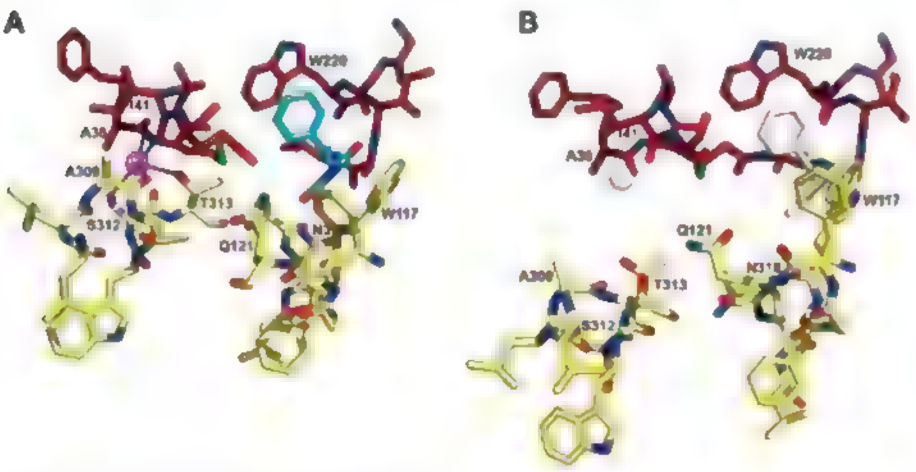

Fig. 2. Comparison of the sodium and substrate binding sites in the occluded and inward-facing structures of Mhp1. **(A)** The occluded state (9). The sodium is colored magenta, and the benzylhydantoin is represented with carbon atoms in cyan. The carbon atoms of the amino acids are colored as in Fig. 1. The interactions between the sodium and neighboring residues are shown with dotted black lines. **(B)** The inward-facing conformation. The amino acids are colored as in (A). The positions of the sodium and benzylhydantoin are represented as in Fig. 1. In this conformation, Thr^{313} and Ser^{312} would not be within liganding distance of a sodium at this position.

Fig. 3. Accessibility of the sodium and substrate binding sites in different states of the transport cycle, as defined by equilibrium MD simulations. Mhp1, colored as in Fig. 1, is shown embedded in the lipid bilayer (gray), with part of the hash motif removed (TM 4 and parts of TM 3 and TM 8) to afford a view of the central cavity. The cyan wire mesh represents the solvent contoured at 20% of the bulk density. Sodium is shown in magenta. **(A)** In the outward-facing state, the central cavity is accessible from the extracellular side. **(B)** In the occluded state, the bound benzylhydantoin and the sodium ion, together with a few water molecules, are isolated in the central cavity. **(C)** In the inward-facing state, the pathway to the extracellular side is sealed and the sodium ion is released into the cytosol as shown by an overlay of the sodium ion positions from six independent MD trajectories (magenta).

Substrate binding site. A large cavity on the inward-facing side of the protein is made up of the neighboring surfaces of TMs 1, 3, 5, 6, and 8 (Fig. 1B and fig. S2). This cavity connects the substrate and cation binding sites that were identified in the occluded and outward-facing conformations (9) with the inside of the cell. The substrate binding site is located between TMs 1, 3, 6, and 8. In the occluded structure, the substrate is sandwiched between the side chains of Trp^{117} on TM 3 and Trp^{220} on TM 6 (Fig. 2). Gln^{121} on TM 3 and Asn^{318} on TM 8 are also in close proximity to the ligand. In changing to the inward-facing structure, large-scale conformational changes result in Trp^{117} moving slightly into the binding site and Gln^{121} and Asn^{318} moving away. These changes would substantially perturb the site and potentially impair the ligand binding ability.

Sodium binding site. The Na^+ binding site is located at the interface of TMs 1 and 8. In the outward-facing structure, the cation interacts with the carbonyl oxygen atoms of Ala^{38} and Ile^{41} of TM 1 and the carbonyl oxygen of Ala^{309} and the side chains of Ser^{312} and Thr^{313} of TM 8 (Fig. 2). In the inward-facing structure, on the other hand, TM 8 has moved ~4.5 Å away from TM 1 so that the Na^+ binding site is no longer intact (Fig. 2), which is reminiscent of the situation in the inward-facing vSGLT structure (8). In the electron density maps, we observe an elongated feature at this site (fig. S3). The density is unlikely to be a Na^+ ion because of its shape and its peak height (8 σ). The use of anomalous diffraction failed to help identify the molecule: no significant peaks were observed in an x-ray fluorescence spectrum (26) (excited at 14 keV), and no peaks were observed at this position in an x-ray anomalous difference Fourier map from data collected at 0.9791 Å. One interesting hypothesis is that this molecule is trapping Mhp1 in the inward-facing conformation. This site could be a potential binding site for inhibitors of the "LeuT superfamily" transporters, the subject of further studies.

Molecular dynamics simulations of sodium binding. To investigate whether this perturbed site in the inward-facing conformation can still bind Na^+, multiscale molecular dynamics (MD) simulations were performed (Fig. 3) (24). For the simulations, the Mhp1 molecules in three dif-

ferent conformations were placed in a nativelike membrane composed of a 4:1 molar ratio of 1-palmitoyl-2-oleoylphosphatidylethanolamine (POPE) and 1-palmitoyl-2-oleoylglycero-3-phosphoglycerol (POPG) lipids (Fig. 3). The observed atomic Cα root mean square (RMS) fluctuations range from 0.5 Å for rigid secondary structural elements to 4 Å for mobile loops (fig. S4). Likewise, the RMS deviations (RMSDs) from the starting structure range from 1.5 to 3 Å after 100 ns. These values are comparable with those for simulations of other high-resolution membrane proteins (*24*). In the multiple MD simulations of the inward-facing structure, sodium initially located in the binding site very rapidly (<2 ns) diffuses into the bulk water on the intracellular side of the protein through a large aqueous pathway between the bundle and the flanking region (Fig. 3C). Such rapid Na^+ release is in marked contrast to similar simulations carried out on the occluded structure where the Na^+ remained in its binding site for over 100 ns with only small variations in bond lengths to the ligating carbonyl oxygen atoms. In the outward-facing state without benzylhydantoin, an exit event was observed only after 18 ns in just one of three 100-ns simulations. We conclude from both structural and dynamic considerations that the Na^+ binding site is intact in the outward-facing and occluded forms and disrupted in the inward-facing form. The presence of benzylhydantoin in its binding site blocks the pathway of the sodium ion to the extracellular side in the simulations and thus couples Na^+ binding with substrate binding as shown in our earlier fluorescence quenching experiments (*9*). Recent simulations of sodium release from vSGLT arrive at similar conclusions for this structural homolog of Mhp1 (*27*).

Conformational differences. Previously (*9*), we reported that, in going from the outward-facing to the occluded state, only TM 10 and the preceding loop show any large-scale difference in conformation. Between the occluded and inward-facing conformations, however, we observe much more dramatic changes (Fig. 4A) resulting in an RMSD in the positions of all pairs of Cα atoms of the two structures of 3.3 Å so that it resembles much more the conformation of the inward-facing structure of vSGLT (*8*) rather than the outward-facing LeuT (*7*). The major changes are primarily due to a rigid body movement of the hash motif relative to the bundle. The C-terminal helices (TMs 11 and 12) move only slightly with respect to the bundle. Consistent with a rigid body movement, the respective residues of the bundle from the three conformations superpose very well with an RMSD of 0.7 Å (fig. S5B). Likewise, the residues in the hash motif from the three conformational states are very similar (RMSD 0.9 Å) (fig. S5C), as are the C-terminal helices (RMSD 0.9 Å) (fig. S5D).

The transition from outward-facing to inward-facing conformations has been analyzed for the LeuT family of transporters in terms of two gating models (*20*). "Thin gates" involving only a few residues control the opening and closing of the substrate binding site to the exterior or interior of the cell, and a "thick gate," so called because of the 20 Å barrier blocking the substrate binding site from the cytoplasm in the outward-facing structure, controls the transition of the protein

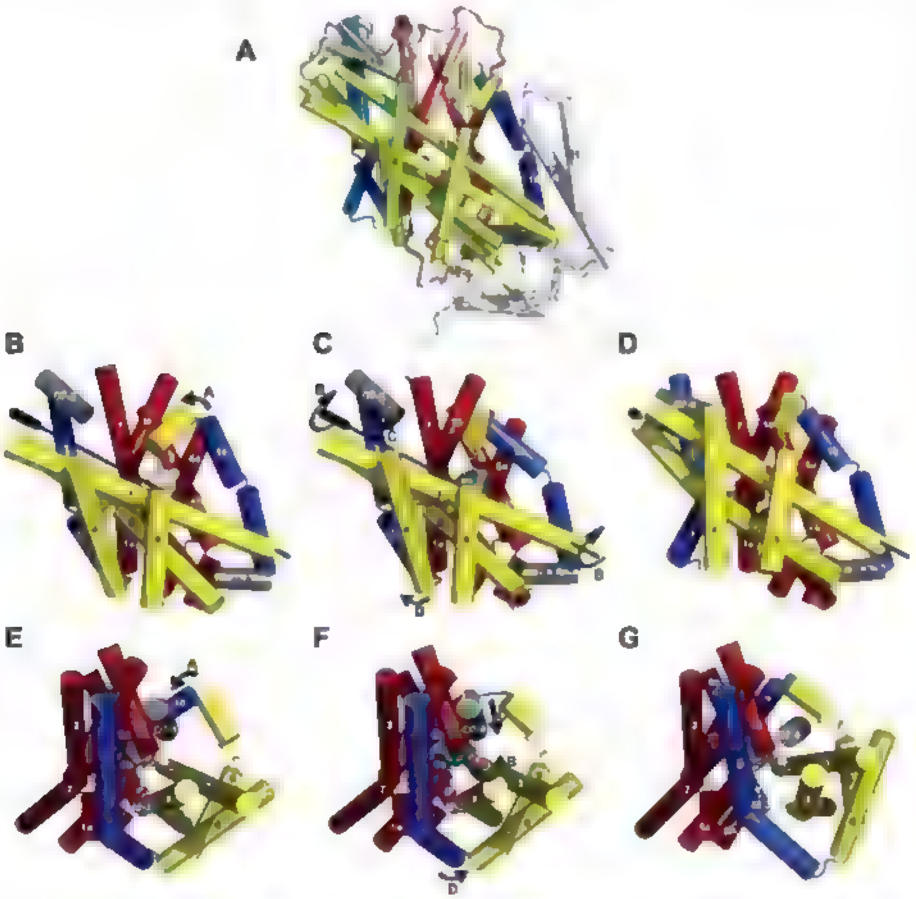

Fig. 4. Conformational changes in Mhp1. **(A)** Overall superposition of the two structures. The outward-facing structure has been colored as in Fig. 1. The inward-facing structure is shown in salmon for the bundle, light green for the hash motif, and light blue for TMs 5 and 10. **(B** to **G)** Two views of the three crystal structures [outward-facing (B and E), occluded (C and F), and inward-facing (D and G)], with arrows representing the conformational changes in moving from one to the other. TMs 11 and 12 and loop regions have been omitted for clarity. In going from outward to occluded, the N-terminal part of TM 10 packs over the substrate (arrow A). From occluded to inward, a 30° rotation of the hash motif relative to the bundle (arrow B) effectively switches the protein from outward- to inward-facing. At the same time, helix OUT 7-8 moves into the extracellular cavity (arrow C), and the N-terminal part of TM 5 (complementary to the N-terminal part of TM 10) moves out to open the intracellular cavity further. The rotation axis is shown by a black line in (B) to (D). The bulge at the tip of this line on the outward face of the protein is the black dot in (E) to (G), where the viewpoint is along the rotation axis. The sodium and benzylhydantoin have been colored as in the previous figures.

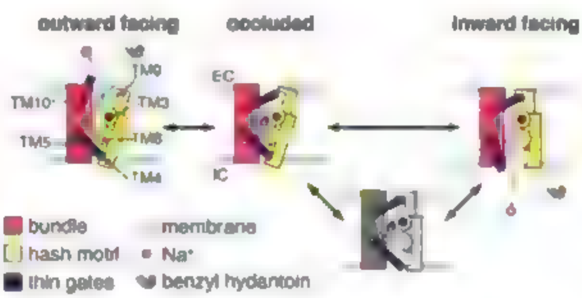

Fig. 5. Schematic representation of the alternating access model in Mhp1, highlighting the thick and thin gates. The three diagrams colored as in Fig. 1 represent the outward-facing, occluded and inward-facing crystal structures. The black-and-white diagram shows another possible state. Upon sodium and substrate binding, the extracellular thin gate (TM 10) closes to form the occluded state. The thick gate then opens with a rigid body rotation of TMs 3, 4, 8, and 9 (the hash motif) relative to TMs 1, 2, 6, and 7 (the bundle). Either independently or concomitantly with this, the intracellular thin gate (TM 5) also opens to allow the substrates to exit toward the cytoplasm. (See also movies S1 to S3.)

from the outward to the inward states. Based on the three structures of Mhp1, the conformational changes involved in these transitions can be described in terms of these gating models as follows.

The first step is the change of the outward-facing state to the occluded state (Figs. 4 and 5). In Mhp1, the outward-facing cavity is formed by TMs 1, 3, 6, 8, and 10 (Fig. 4). The N-terminal end of a flexible helix, TM 10, acts as an extracellular "thin" gate folding over the substrate as it binds to close the outward-facing cavity, partially sealing it from the exterior. This is followed by a change of the occluded state to the inward-facing state. Here, the hash motif (TMs 3, 4, 8, and 9) acts as the thick gate undergoing a rotation of 30° with respect to the bundle (concomitant with a translation of 3 Å) around an axis 40° to the plane of the membrane (Fig. 4). With this movement of the hash motif, the part of the outward-facing cavity that still remains after one side is closed by the extracellular flexible TM 10 is completely filled by the C termini of TMs 3 and 9 and a small extracellular helix (OUT 7-8) (Fig. 1); meanwhile, the movement of TMs 4 and 8 opens the ion and substrate binding sites toward the cytoplasm, forming an inward-facing cavity. At the same time, the intracellular "thin gate" made of the flexible helix TM 5 bends to open this cavity further (Fig. 4). TM 5 is the pseudo two-fold equivalent of the extracellular "thin gate" TM 10.

Molecular dynamics simulations of the conformational changes. To evaluate these proposed conformational changes, the transition from the outward-facing conformation through the occluded state to the inward-facing structure has been simulated using dynamic importance sampling (DIMS) MD (*24*, *28*) (movie S1 and fig. S6). The simulations demonstrate that no large steric or energetic barriers occur to hamper this transition (fig. S7). Equilibrium simulations, on the other hand, show that the thin gates can sample conformations near their open and closed states regardless of the starting conformations (fig. S8). It is likely, therefore, that the action of the thin gates is partially a stochastic process, occurring on the time scale of a few hundred nanoseconds. In the simulations, movement of the intracellular thin gates was largely independent of the movement of the thick gate. The conformation of the extracellular thin gate, however, is coupled to the thick gate by the movement of TM 9 toward the bundle, which locks the extracellular gate into its closed position (fig. S9). MD simulations started in the inward-facing conformation (thick gate closed to the outside) only sample the extracellular closed gate region, because the movement of the extracellular gate (TM 10) is restricted. In contrast, in simulations beginning with the occluded state, the extracellular gate can partially open (fig. S8). Similarly, the movement of the intracellular gate to the outside (TM 5) is restricted when the thick gate is open (fig. S8). No spontaneous transition was observed for the thick gate within a total of 1.6 μs of simulations. Thus, it appears that the action of the thick gate becomes the rate-limiting step of the transport process, with the thin gates modulating much faster access and egress of substrates.

Transport mechanism. With the recent elucidation of the various structures belonging to the LeuT superfamily, there has been much speculation on the conformational changes necessary for the protein to switch from the outward to the inward conformations. As discussed recently (*19*, *20*), essentially two mechanisms have been proposed. The first (*7*, *10*) involves the flexing of the extended TMs 1 and 6 of the bundle. These helices have been seen to bend in going from the occluded structure of LeuT (*29*) to an open inhibitor-bound structure and between the outward open and occluded forms of AdiC (*21*). In the second mechanism (*9*, *30*, *31*), these helices would remain rigid and instead the bundle and flanking helices would move relative to one another. In the structures of Mhp1, there is no substantial change in conformation of TMs 1 and 6. Instead, the structures are much more consistent with the rocking-bundle mode first suggested by Forrest *et al.* (*30*), where the 10 TM core of the protein could be split into the "bundle" (TMs 1, 2, 6, and 7) and the "scaffold" (TMs 3, 4, 5, 8, 9, and 10), with the bundle and scaffold rocking relative to each other to alter the conformation from outward to inward. There are, however, some differences between that model and the observations on Mhp1. Analyses of which helices differ among the three structures of Mhp1, together with the MD simulations in a nativelike bilayer, show that the bundle (TMs 1, 2, 6, and 7) and hash motif (TMs 3, 4, 8, and 9) move relative to each other as approximately rigid bodies. The helices that form the thin gates (TMs 5 and 10), on the other hand, can move independently, although the simulations suggest that they can be locked in place depending on the position of the thick gate. This is shown schematically in Fig. 5 and movies S2 and S3.

It is evident that the details of substrate transport will vary amongst the many transporters of the LeuT superfamily. The occlusion mechanism shown for AdiC, for example, differs substantially from that of Mhp1 (*21*). However, the similarities of the outward-facing structure of LeuT and the inward-facing structure of vSGLT with the corresponding structures of Mhp1, together with the consistency of our model with accessibility measurements on the serotonin transporter (*30*), suggest that the switch between the two conformations is not just limited to Mhp1. It seems, therefore, that the molecular basis of the alternating access model revealed by this study is likely to be common among this expanding superfamily.

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Supporting Online Material

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Unconventional *s*-Wave Superconductivity in Fe(Se,Te)

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The superconducting state is characterized by a pairing of electrons with a superconducting gap on the Fermi surface. In iron-based superconductors, an unconventional pairing state has been argued for theoretically. We used scanning tunneling microscopy on Fe(Se,Te) single crystals to image the quasi-particle scattering interference patterns in the superconducting state. By applying a magnetic field to break the time-reversal symmetry, the relative sign of the superconducting gap can be determined from the magnetic-field dependence of quasi-particle scattering amplitudes. Our results indicate that the sign is reversed between the hole and the electron Fermi-surface pockets ($s_\pm$-wave), favoring the unconventional pairing mechanism associated with spin fluctuations.

The discovery of iron-based superconductors (*1*) triggered efforts to elucidate the mechanism of electron pairing responsible for a superconducting (SC) transition temperature of 55 K (*2*). Superconductivity in iron-based compounds occurs in close proximity to a magnetic order (*3*), invoking a pairing mechanism associated with spin fluctuations (*4*–*7*). The most fundamental information to identify the mechanism of pairing is the structure of SC-gap function, a measure of the strength and the quantum mechanical phase of electron pairs in momentum (*k*) space. Although the SC-gap function of conventional phonon-mediated superconductors has the same sign all over *k* space (*s*-wave symmetry), that of spin fluctuation–mediated superconductors is expected to exhibit a sign reversal between the Fermi momenta connected by the characteristic wave vector **Q** for spin fluctuations (*8*). As a consequence of the sign reversal, nodal planes in which the SC gap vanishes should exist in *k* space. If such nodal planes intersect the Fermi surface, low-energy quasi-particle (QP) states will emerge near the nodes.

In the case of iron-based superconductors, however, the presence of multiple bands at the Fermi level makes the situation much more complicated and exotic because the Fermi surface consists of disconnected two-dimensional hole and electron pockets centered at Γ and M points, respectively (Fig. 1A) (*9*). Because the hole and the electron pockets are similar in both shape and volume, the inter-band nesting between these pockets may generate spin fluctuations at $\mathbf{Q} = (\pi, 0)$ (in a Brillouin zone defined by the unit cell containing one iron). If such a spin fluctuation is responsible for the electron pairing, a sign reversal of the SC-gap function occurs between the hole and the electron pockets, resulting in $s_\pm$-wave symmetry (*4*–*7*).

The low-energy QP excitation spectrum of $s_\pm$-wave superconductor, however, is indistinguishable from those of conventional *s*-wave superconductors because the nodal planes do not exist on the Fermi pockets. Indeed, penetration depth measurement (*10*) and angle-resolved photoemission spectroscopy (*11*, *12*) suggest that the amplitude of the SC gap is finite all over the Fermi surfaces. In order to distinguish an unconventional $s_\pm$-wave from a conventional *s*-wave, the relative sign of the SC gap between the hole and the electron pockets must be determined by means of a phase-sensitive experiment (*13*).

We used a spectroscopic-imaging scanning tunneling microscopy (SI-STM) technique to measure the tunneling conductance as a function of energy at every pixel of the STM image. If the experiments are performed at low enough temperatures, each tunneling spectrum reflects QP density of states from which one can infer whether or not the nodal planes intersect the Fermi surface. By analyzing the data by use of Fourier transformation, *k*-resolved information on QP states can be obtained (*14*–*16*). Also, the data under the magnetic field contain information on the relative sign of the SC-gap function (*16*). By combining these, the structure of the SC gap can then be determined unambiguously.

We performed SI-STM experiments on single crystals of Fe(Se,Te) with transition temperatures of T_c = 13 to ~14.5 K (*13*). Fe(Se,Te) has the simplest crystal structure among the various iron-based superconductors, consisting of only Fe(Se,Te) layers (*17*). The single crystals were cleaved so as to expose clean and flat surfaces, which were expected to be electronically neutral, minimizing the surface reconstruction. In a typical topographic image of a cleaved surface (Fig. 2A, inset), we imaged a square lattice with defects. The lattice constant was estimated to be ~3.8 Å, which is in good agreement with the inter-chalcogen distance. There are several bright spots in the image that probably represent excess iron atoms, which is in agreement with previous reports (*18*, *19*).

The SC gap was identified in the tunneling spectra (Fig. 2B). At 0.4 K, the spectral weight is completely removed over a finite energy range near the Fermi energy, and instead very sharp gap-edge peaks grow at ~±1.7 meV. These features—characteristics of full-gap superconductivity—strongly suggest that there is no node in the SC-gap function on the Fermi surface. At elevated temperatures, the SC gap is smeared out and eventually disappears at about 11 K, which is somewhat lower than a bulk T_c ~ 14.5 K, presumably because of a spatial distribution of T_c inside the sample. Below T_c, additional structures can be seen outside the gap-edge peaks (around ~±4 meV), which are not symmetric about the Fermi level. The origin of these structures is unclear at present.

To explore QP states in *k* space by using SI-STM, we needed to detect QP interference (QPI) effect by means of Fourier analyses of

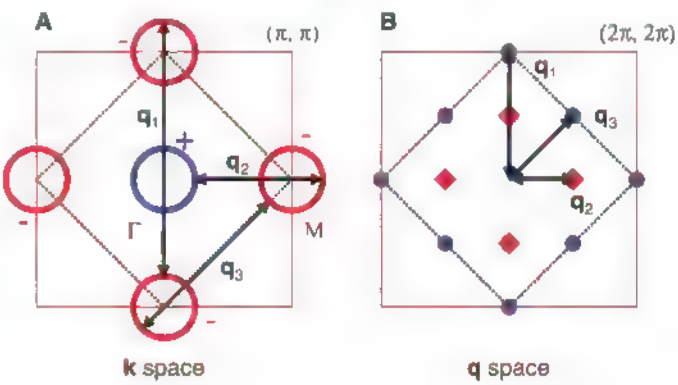

Fig. 1. Schematic of reciprocal-space electronic states of an iron-based superconductor. **(A)** Fermi surface and inter-Fermi-pocket scatterings in *k* space. According to a band calculation (*9*), there are two hole cylinders and two electron cylinders around Γ and M points, respectively. For simplicity, two Fermi cylinders are represented by one circle. The black dotted diamond denotes the crystallographic Brillouin zone, and the red square indicates the "unfolded" Brillouin zone defined by the unit cell containing one iron atom. Signs of the SC gap expected for $s_\pm$-wave symmetry are shown by different colors. The arrows denote inter-Fermi-pocket scatterings. $\mathbf{q}_2$ and $\mathbf{q}_3$ connect different pockets, whereas $\mathbf{q}_1$ is an umklapp process. **(B)** Expected QPI spots in **q** space associated with inter-Fermi-pocket scatterings. Blue filled circles and red filled diamonds represent sign-preserving and sign-reversing scatterings, respectively, for the $s_\pm$-wave SC gap. The former will be enhanced by a magnetic field, whereas the latter may be suppressed (*16*).

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spectroscopic images (*14–16*). In the presence of defects in the sample, QPs are scattered and interfere with each other, generating electronic standing waves modulated with QP scattering vector **q** in real space. If the excitation energy E is low enough as compared with the Fermi energy, **q** connects different k points on the Fermi surface. Because of the presence of disconnected Fermi-surface pockets around the Γ and M points, the dominant QP scattering vectors may include the inter-Fermi-pocket scatterings $\mathbf{q}_1$, $\mathbf{q}_2$, and $\mathbf{q}_3$ (Fig. 1A), which can be observable in **q** space (Fig. 1B) by performing Fourier analyses of QPI patterns. Here, $\mathbf{q}_1$ connects the same pocket, representing the umklapp scattering. The remaining vectors $\mathbf{q}_2$ and $\mathbf{q}_3$, which bridge different Fermi-surface pockets, are important to discussion of the phase relationship between the hole and the electron pockets.

In order to image the standing waves associated with QPI, we collected the tunneling conductance $g(\mathbf{r}, E)$, where **r** is the position at the surface. We then mapped a ratio $Z(\mathbf{r}, E) \equiv g(\mathbf{r}, +E)/g(\mathbf{r}, -E)$. This ratio-taking process has a twofold purpose (*15*, *20*). First, any extrinsic effects associated with the feedback loop so as to stabilize the tip-sample separation are removed (*20*). Second, QPI of Bogoliubov QPs should be particle-hole symmetric, namely $\mathbf{q}(+E) = \mathbf{q}(-E)$, and the modulations at $+E$ should be out of phase spatially with the modulations at $-E$ (*15*, *21*). The ratio-taking process naturally extracts particular modulations fitting these constraints.

The QPI experiments were performed at 1.5 K in the same field of view shown in Fig. 2A. As seen in Fig. 3A, $Z(\mathbf{r}, E)$ shows patchy domains of a length scale of a few nanometers, within which horizontal and vertical periodical streaks can be recognized. The streaks were rotated by 45° with respect to the atomic rows in Fig. 2A. These modulations with periodicity of twice the nearest iron-iron distance give rise to the broad peaks at $\mathbf{q}_2$ in the Fourier map $Z(\mathbf{q}, E)$ (Fig. 3B). Weak but clear peaks appear at $\mathbf{q}_3$ as well. Thus, the two scattering processes connecting different Fermi pockets were observed. The pronounced contrast of intensities between $\mathbf{q}_2$ and $\mathbf{q}_3$ (Fig. 3B) might suggest that the two processes are different in character.

The intensity of the QPI is influenced strongly by the relative sign of the SC gap between the two Fermi pockets involved in the respective scattering, through the coherence factor $C(\mathbf{q})$ representing the pairing of electrons. This gives rise to a phase-sensitive **q** selectivity for the QPI (*16*, *22*, *23*), which depends on the time-reversal symmetry of scattering potential. For scalar potential scattering that is even under time reversal, $C(\mathbf{q}) \sim 0$ if **q** connects the states with the same sign of the SC gap. As a result, the QPI intensity, which is proportional to $C(\mathbf{q})$, will appear only at sign-reversing momenta. For magnetic scattering that is odd under time reversal, the situations are opposite to scalar potential, $C(\mathbf{q}) \sim 0$ if **q** connects the states with the opposite sign of the SC gap. If the SC gap is spatially inhomogeneous, Andreev scattering would also contribute to QPI. Similarly to magnetic scattering, $C(\mathbf{q})$ of this process diminishes for sign-reversing momenta (*16*, *22*, *23*).

Once we know the nature of the QP scatterers, the phase-sensitive **q** selectivity for QPI provides an opportunity to highlight the relative sign of SC gaps in the Fourier-transformed QPI patterns (*16*, *22*, *23*). Similar ideas have also been proposed theoretically (*24–26*). In practice, however, various QP scatterers inevitably coexist in the same sample. To use the phase-sensitive **q** selectivity for QPI, we needed to intentionally introduce scatterers that activate only either sign-reversing or sign-preserving scatterings.

As a source of extra scattering with well-defined **q** selectivity, we used magnetic-field effects (*16*, *22–24*). The magnetic field breaks the time-reversal symmetry and gives rise to vortices. Therefore, extra time reversal–odd scatterings may be generated, and also the sup-

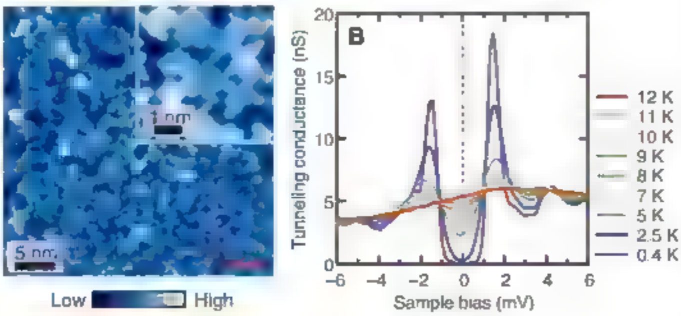

Fig. 2. STM characterization of Fe(Se, Te). **(A)** Topographic image of the sample with $T_c \sim 13$ K taken at 1.5 K. The setup conditions for imaging were a sample-bias voltage of –20 mV and a tunneling current of 0.1 nA. Red arrows denote directions of the nearest iron-iron bond. The excess iron atoms are imaged as bright spots. (Inset) Magnified image showing an atomic lattice of chalcogens. **(B)** Temperature dependence of the tunneling spectrum examined at the same location 7 nm apart from the nearest iron atom. Data were collected for the sample with $T_c \sim 14.5$ K. The residual spectral weight at the Fermi energy is negligibly small, indicating that the SC gap is finite everywhere on the Fermi surface. Data were taken with a sample-bias voltage of –20 mV and a tunneling current of 0.1 nA. Bias-modulation amplitude was set to 0.1 $\mathrm{mV_{rms}}$.

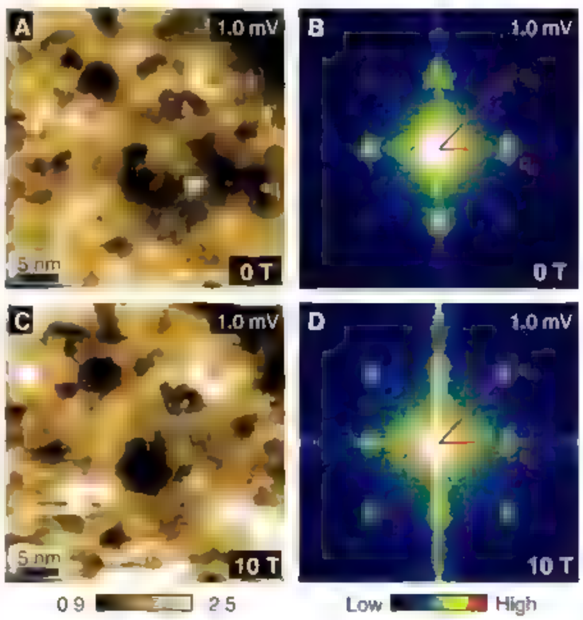

Fig. 3. Magnetic field–dependent QPI patterns of Fe(Se, Te). **(A)** Real-space QPI pattern imaged by mapping the conductance ratio $Z(\mathbf{r}, E = 1$ meV). Setup conditions were a sample-bias voltage of –20 mV and a tunneling current of 0.1 nA. Bias-modulation amplitude was set to 0.5 $\mathrm{mV_{rms}}$. **(B)** $Z(\mathbf{q}, E = 1$ meV) obtained by taking a Fourier transformation. In order to enhance the signal-to-noise ratio, the original $Z(\mathbf{q}, E = 1$ meV) map is averaged by folding it so as to superimpose the equivalent **q** positions. QPI signals are observed at two **q**s corresponding to the inter-Fermi-pocket scatterings $\mathbf{q}_2$ and $\mathbf{q}_3$. **(C** and **D)** $Z(\mathbf{r}, E = 1$ meV) and $Z(\mathbf{q}, E = 1$ meV) under a magnetic field of 10 T, respectively. QPI signals in **q** space exhibit prominent magnetic-field dependence. These experiments were carried out in the same field of view as Fig. 2A.

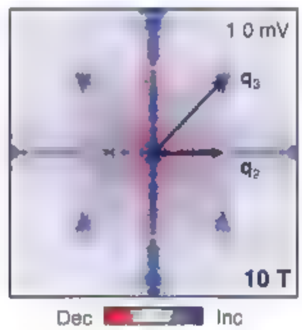

Fig. 4. Magnetic field–induced change in QPI intensities indicates the $s_{\pm}$-wave symmetry. Difference between $Z(\mathbf{q}, E = 1$ meV) maps with and without a magnetic field is shown by subtracting Fig. 3B from Fig. 3D. It is clear that signals at $\mathbf{q}_2$ and $\mathbf{q}_3$ exhibit totally opposite behavior, indicating that these two scatterings have different characters. This pattern can only be explained if the SC gap possesses $s_{\pm}$-wave symmetry (*13*).

pression of a SC gap at the center of vortices may induce Andreev scattering (*16*, *22*, *23*). In both cases, scatterings with sign-preserving momenta should be selectively enhanced, as discussed above. In addition to such **q**-selective enhancement of QP scatterings, there may be a **q**-independent overall reduction of QPI intensity under magnetic fields; a Doppler shift of QP energies induced by supercurrent around vortices has been argued to suppress QPI amplitude irrespective of the nature of the scatterings (*16*, *22*, *23*). In total, sign-preserving and sign-reversing scatterings will be enhanced and suppressed, respectively, by a magnetic field. This technique was successfully applied in the detection of the *d*-wave SC-gap function in a cuprate superconductor (*16*).

In the case of $s_{\pm}$-wave symmetry, $\mathbf{q}_2$ connects Fermi pockets with the opposite sign of the SC gap (sign-reversing scattering), whereas $\mathbf{q}_3$ does Fermi pockets with the same sign (sign-preserving scattering) (Fig. 1A). Therefore, intensities of QPI at $\mathbf{q}_2$ and $\mathbf{q}_3$ should be suppressed and enhanced, respectively, with application of the magnetic field. If the gap symmetry were of a *d*-wave or conventional *s*-wave, the magnetic-field dependence of intensities of QPI at $\mathbf{q}_2$ and $\mathbf{q}_3$ would be qualitatively different from that expected for $s_{\pm}$-wave symmetry (*13*).

Shown in Fig. 3, C and D, are $Z(\mathbf{r}, E)$ and $Z(\mathbf{q}, E)$, respectively, under a magnetic field of 10 T applied perpendicular to the surface. Both scatterings at $\mathbf{q}_2$ and $\mathbf{q}_3$ show field dependence. In the field-induced change in $Z(\mathbf{q}, E)$ (Fig. 4), an opposite-field dependence is clearly observed between the two scatterings, the intensity at $\mathbf{q}_2$ is suppressed by a field, whereas that at $\mathbf{q}_3$ is enhanced, which was observed at all E studied (< 5 meV) and pronounced at 1 to ~3 meV near the edge of the SC gap (*13*). These observations are exactly what are expected for $s_{\pm}$-wave symmetry, implying that the sign of the SC gap is reversed between the Fermi pockets around Γ and M points, whereas adjacent M-point Fermi pockets have the same sign. With the support of the fully gapped behavior of QP density of states demonstrated in Fig. 2B, we conclude that only $s_{\pm}$-wave symmetry is consistent with the SI-STM data.

The sign reversal in the SC-gap function implies that the electron pairing is mediated by repulsive interaction in *k* space (*8*), which is most likely spin fluctuations associated with the nesting between the Fermi pockets (*4*–*7*). It was theoretically pointed out in models based on spin fluctuations that $s_{\pm}$-wave is not the only possible symmetry in iron-based superconductors; *d*-wave and nodal $s_{\pm}$-wave symmetries may be stabilized within the same theoretical framework, depending on the details of the band structure (*27*, *28*). Experimentally, nodal superconductivity has indeed been suggested for LaFePO and $BaFe_2(As_{1-x}P_x)_2$ (*29*, *30*). It should therefore be meaningful to establish the phase structure of the SC-gap function in these materials by using the *k*-resolved phase-sensitive QPI technique to step further toward understanding the pairing mechanism of iron-based superconductors.

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Mechanism and Kinetics of Spontaneous Nanotube Growth Driven by Screw Dislocations

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Single-crystal nanotubes are commonly observed, but their formation is often not understood. We show that nanotube growth can be driven by axial screw dislocations: Self-perpetuating growth spirals enable anisotropic growth, and the dislocation strain energy overcomes the surface energy required for creating a new inner surface forming hollow tubes spontaneously. This was demonstrated through solution-grown zinc oxide nanotubes and nanowires by controlling supersaturation using a flow reactor and confirmed using microstructural characterization. The agreement between experimental growth kinetics and those predicted from fundamental crystal growth theories confirms that the growth of these nanotubes is driven by dislocations.

The question of how one-dimensional (1D) crystals grow has long fascinated scientists, starting from microscale whiskers (*1*, *2*) and continuing on to nanowires (NWs) (*3*, *4*). One-dimensional growth of NWs has been explained by the vapor-liquid-solid (VLS) mechanism (*2*, *3*) and other catalyst-driven mechanisms (*4*). The growth mechanism of frequently observed single-crystal nanotubes (NTs) (*5*) is usually thought to be unrelated to that of NWs. However, NWs can also grow via the propagation of an axial screw dislocation (*1*, *6*–*8*). Recent theoretical work has connected the growth rate of a carbon nanotube to the magnitude of the Burgers vector of a screw dislocation that it possesses (*9*). We used dislocation-driven growth to rationally grow inorganic nanotubes from solution and to explain the driving forces behind the formation of hollow tubes.

Dislocation-driven anisotropic 1D crystal growth is explained by preferred growth at the self-perpetuating spirals of axial screw disloca-

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tions under low supersaturations (*1*, *6*). Here, supersaturation (σ) is defined as

$$\sigma = \ln\left(\frac{c}{c_0}\right) \quad (1)$$

where c and c_0 are the concentration and equilibrium concentration of the system, respectively (*10*). According to classical crystal growth as described by the Burton-Cabrera-Frank (BCF) theory (*11*), dislocation growth, layer-by-layer (LBL) growth, and dendritic growth progressively dominate crystal growth as supersaturation is increased (fig. S1) (*10*, *11*). Therefore, intentionally exploiting low supersaturation conditions that favor the dislocation-driven growth mechanism could provide a pathway to enable catalyst-free synthesis of 1D nanomaterials. Specifically, by using flowed aqueous solutions of constant low supersaturation, we demonstrate dislocation-driven growth of single-crystal NWs and hollow NTs of zinc oxide (ZnO) in solution-phase. We show that axial screw dislocations with large magnitude contained within these materials result in the spontaneous formation of single-crystal NTs as the equilibrium morphology of 1D nanomaterials.

We chose ZnO (zincite) as a model material partly because 1D nanomaterials of semiconducting ZnO have found many applications, such as in photonics (*12*) and solar (*13*) and piezoelectronic (*14*) energy conversion, and they can be readily grown in solution (*15*, *16*). ZnO also has well-characterized dislocation microstructure (*17*). In typical aqueous synthesis, zinc salts are hydrolyzed in closed containers in the presence of weak polyamine bases, such as hexamethylenetetramine (HMT), producing ZnO NWs, nanorods (NRs) (*15*, *16*), and even NTs or microtubes (*18*, *19*). Nanostructure morphology is influenced by variations in reagent concentration, growth time, and temperature (*16*). To investigate the possibility that growth is driven by axial screw dislocations, we observe the effect of supersaturation on nanomaterial morphology and growth kinetics using the zinc nitrate and HMT reaction. However, commonly practiced closed-system hydrothermal growth of ZnO, where precursors are introduced at once and allowed to react to completion, suffers from a significant decline in the concentration of soluble zinc species during the course of the reaction (fig. S2). Such changes in the supersaturation conditions lead to irregular growth kinetics that are difficult to deconvolute and may affect morphology. We therefore developed a continuous flow reactor (CFR) (fig. S3) (*20*) to maintain constant supersaturation and enable indefinite reaction times.

We observed a dramatic morphology dependence of the growth products on supersaturation. Specifically, when CFR experiments are run at decreasing precursor concentrations from millimolar (mM) down to micromolar (μM) (*20*), a steady decrease in diameter and an increase in aspect ratio of the resulting 1D ZnO nanomaterials is observed (Fig. 1, A to C). High concentrations (10 mM) yield NRs of about 270 nm in diameter with clear tapering (Fig. 1A), rather similar to what are observed in closed-system growth (fig. S11E). Intermediate concentrations (500 μM) produce NWs of about 100 nm in diameter (Fig. 1B), and the lowest concentrations (30 μM) yield high-aspect-ratio nanostructures of about 22 nm in diameter (Fig. 1, C to F). These nanomaterials were confirmed to be of the single-crystal wurtzite structure with growth along the [001] direction by transmission electron microscopy (TEM) (Fig. 1, D and F; only data for low-concentration NWs shown) and electron diffraction (ED) (Fig. 1E, inset). In all cases, seed nuclei were first created in a separate high-concentration (100 mM) nucleation step (*20*). This is important for the extremely low-concentration reactions (Fig. 1, C to E) that are below the concentration necessary for heterogeneous nucleation. Occasionally, these seeds are visible at the bases of NWs synthesized at the lowest concentration (Fig. 1F). Interestingly, they have a coherent crystal lattice with the NWs but contain more

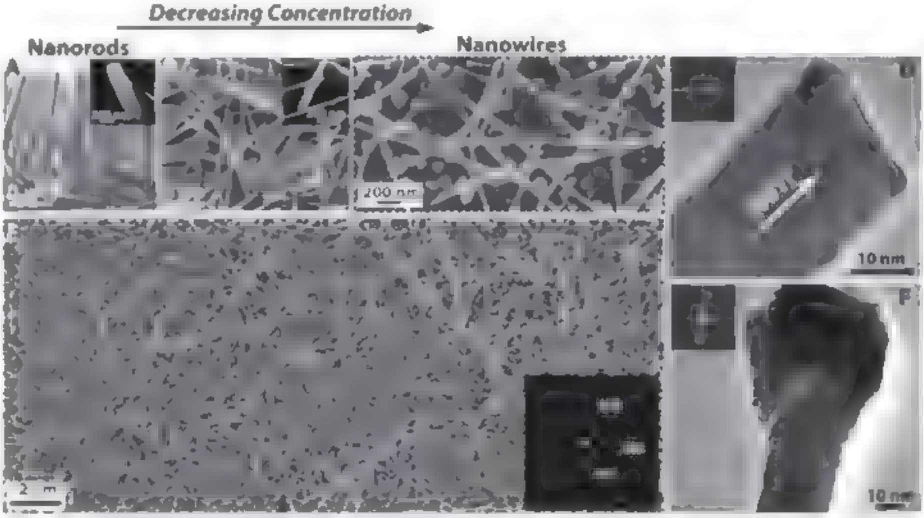

Fig. 1. Evolution of ZnO morphology with decreasing precursor concentration (supersaturation). Scanning electron micrographs of ZnO morphology evolution, from NRs/NWs (**A** and **B**, run at concentrations of 10 mM and 500 μM, respectively) to high-aspect-ratio ZnO NWs (**C** and **E**, run at 30 μM), as supersaturation is decreased in the CFR. The electron diffraction pattern along [100] zone axis [inset in (E)] confirms that the NWs are zincite. The NWs (E) grow along the [001] direction as indicated by high-resolution TEM (**D**) and form continuous crystals with the seed nuclei as shown in TEM (**F**). The corresponding fast Fourier transform images are shown in the (D) and (F) insets.

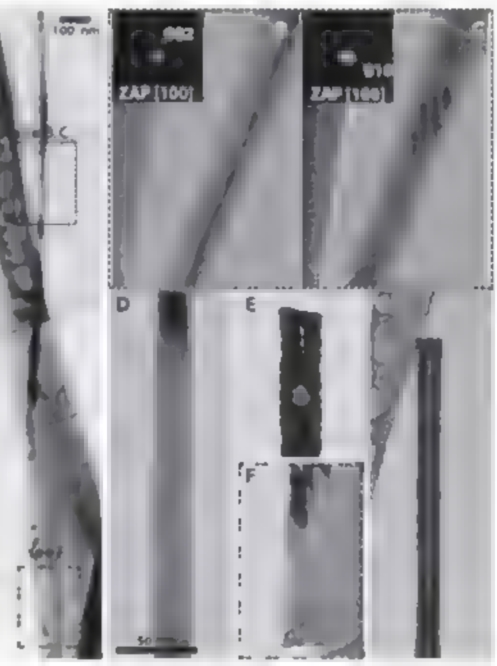

Fig. 2. TEM observation of screw dislocations within ZnO NWs and the crystal behavior of NTs. Several TEM images of a ZnO NW are tiled together to provide perspective of the areas examined (**A**). Exciting the (002) spot in the [100] zone axis pattern (ZAP) shows dislocation contrast (**B**), whereas exciting the orthogonal (010) spots makes the dislocation invisible (**C**). Because both the growth direction and dislocation direction are along [001], this behavior is consistent with a dislocation of screw character. The amorphous coating in (A) to (C) is carbon deposition from the TEM. Several micrographs succinctly show the variety of possible morphologies, including solid NWs (**D**), the intermediate voided NWs (**E** and **F**), and the hollow NT (**G**), whose forms are dictated by the strength of the dislocation (Burgers vector magnitude). Two cases are shown where the voids are either irregularly (E) or evenly (F) spaced. All images share a 50-nm scale bar except (A).

defects. These defects suggest slight misorientation between adjacent crystal grains that form each seed nuclei and presumably provide a source for dislocations (*21*). Such dislocations could then propagate the NW growth.

We observed axial dislocations in the thin, high-aspect-ratio NWs grown at low concentrations (Fig. 1, C to F) using diffraction contrast TEM. For diffraction contrast images taken along the [100] zone axis (Fig. 2, B and C), dislocation contrast is visible under the two-beam condition that excites the (002) diffraction spot (Fig. 2B), which is along the direction of the dislocation line and NW growth axis. Exciting the orthogonal (010) family of spots, the dislocation becomes invisible (Fig. 2C), consistent with the behavior of a screw dislocation.

Nearly all the products from low-concentration CFR synthesis examined under TEM were not NWs with solid cores such as the one shown in Fig. 2D, but instead voided (Fig. 2, E and F) or hollow NTs (Fig. 2G). Axial screw dislocations contained within NWs not only drive anisotropic growth but also cause the spontaneous formation of NTs due to the dislocation strain energy. Because of the disruption of the perfect periodicity within the crystal lattice, there is a strain energy per unit length (E) due to a screw dislocation that is quadratically dependent on the magnitude of the Burgers vector (b)

$$E = \frac{b^2\mu}{4\pi}\ln\left(\frac{R}{r}\right) \qquad (2)$$

where μ is the shear modulus, and R and r are the outer and inner tube radii, respectively (*22*, *23*). As b increases, eventually the crystal contains enough strain energy that it exceeds the energy cost of creating a new inner surface and the dislocation core becomes hollow. This causes the formation of micropipes often observed in dislocation-prone materials such as SiC or GaN (*22*, *24*). An energy balance between surface energy ($2\pi\gamma r$, where γ is surface energy) and the strain energy from Eq. 2 (both per unit length) results in a relationship between r and b (*22*).

$$b_{TUBE} = \sqrt{\frac{8\pi^2\gamma r}{\mu}} \qquad (3)$$

For NWs reaching this energy threshold, the solid NW becomes a hollow NT, as observed in these ZnO nanostructures (Fig. 2, D to G). Essentially, the equilibrium morphology of 1D nanomaterials whose growth is driven by screw dislocations should be hollow NTs (Fig. 3A) when the Burgers vector is sufficiently large (*25*). It is possible that the intermediate (void) case is on the threshold and oscillates between the solid and hollow conditions due to small fluctuations in growth environment and NW thickness that subtly change the energy balance, or tubes initially formed could partially close up after synthesis.

The strain energy imbalance due to a coaxial screw dislocation in a cylinder also results in a torque around the dislocation known as the Eshelby twist (*26*). This was confirmed in nanowire pine trees of PbS and PbSe (*6*, *7*). For tubes, the Eshelby twist equation must be modified (*27*) from the solid cylinder case to

$$\alpha = \frac{b}{\pi R^2 + \pi r^2} \qquad (4)$$

with α representing lattice twist in radians/length and R and r representing the outer and inner radii of the tube, respectively. Attempts to observe the twist in these ZnO NTs by indexing the zone axis via electron diffraction as the electron beam is moved along the object revealed no Eshelby twist above the detection limits of the technique, which is about 5° of absolute twist (fig. S4) (*20*). We further adopted a finer technique (*28*) of indexing twist contours using dark field TEM (fig. S5) that allowed the estimate of a twist of ~1.6°/μm for these completely hollow thin NTs and ~ 4.5°/μm for solid NWs with larger diameter (~100 nm). Although the amount of twist observed in the larger-diameter solid NWs is in line with the Eshelby prediction, such a small amount of twist in the small diameter NTs was puzzling because Eq. 4 predicts twists of ~100°/μm. This made us realize that the classic dislocation micropipe treatment by Frank was incomplete for 1D NTs because it overlooks the Eshelby twist mechanism for strain energy relief. The very small Eshelby twist in NTs is expected if we consider that there are two competing mechanisms for the alleviation of dislocation strain, (i) forming a hollow core and (ii) producing a torque around the dislocation axis via the Eshelby twist mechanism.

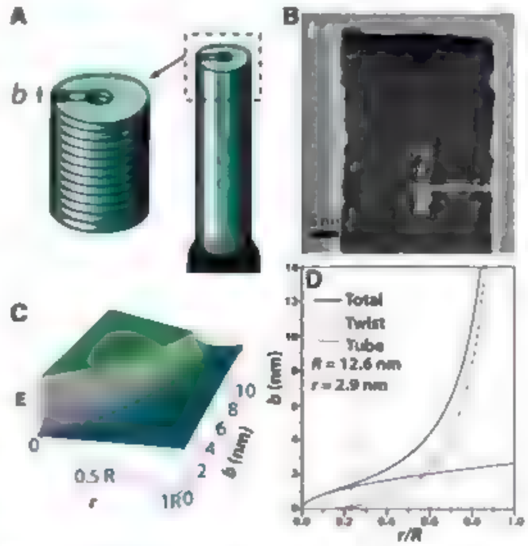

Fig. 3. Two pathways to relieve the strain energy and the estimation of b in ZnO NTs. Large strain energy contained within a screw dislocation coaxial to a nanowire leads to the formation of a NT or voided structure as schematically illustrated (**A**). A HRTEM of the tip of a NT (**B**) allows direct measurement of the critical parameters R, r, and b. The energy for a dislocated ZnO NT (**C**) is shown from Eq. 5 to be dependent on r and b for fixed R. The dashed line represents the energy minimum. By explicitly solving Eq. 5 along this energy valley, we obtain an energy-minimized relation for b versus r/R (**D**) for the specific ZnO NT in (B), where $R = 12.6$ nm, $r = 2.9$ nm, and $b = 1.9$ nm [$r/R = 0.23$, noted by the vertical green line in (D)]. The total contribution to b (Eq. 6) has components due to the hollow inner tube surface energy (Tube) and to the Eshelby twist (Twist). At low Burgers vector, the total effect follows the dislocation hollow core line and almost all strain energy is alleviated by hollowing out the dislocation core. At larger Burgers vector and larger inner core radius, the surface energy becomes large and all new strain energy is relaxed through the Eshelby twist, with the intermediate b transitioning between these two limits.

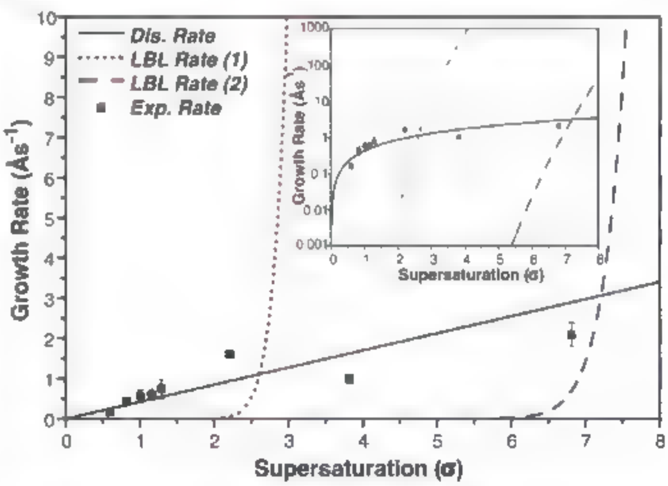

Fig. 4. Summary of experimental and theoretical ZnO crystal growth kinetics. Theoretical growth rates as a function of supersaturation for a dislocation mechanism (solid) and LBL mechanism calculated using a c_0 of 11 μM and physical constants (small dashed line uses a small surface energy value of 0.16 J/m2; large dashed line uses an intermediate surface energy value of 0.31 J/m2) for growth along the c axis of ZnO. Experimental growth rates (squares; error bars show SD) clearly follow the trend predicted by a dislocation mechanism. This is further illustrated by the logarithmic rate plot (inset).

Once the nanostructure becomes hollow, the overall energy per unit length (E) contains three terms: the surface energy from the hollow inner tube, the lattice strain due to the dislocation, and the reduction in lattice strain due to the Eshelby twist.

$$E = 2\pi\gamma r + \frac{\mu b^2}{4\pi}\ln\left(\frac{R}{r}\right) - \frac{\mu b^2}{4\pi}\frac{(R^2 - r^2)}{(R^2 + r^2)} \quad (5)$$

Using ZnO specific values for surface energy, 0.31 J/m^2 (*20*), shear modulus, 44.3 GPa (*29*), and the radii of the NT shown in Fig. 3B allows for an evaluation of this equation. A 3D surface plot of Eq. 5 constructed for E versus b and r/R (Fig. 3C) shows that there is an energy valley (minimum) associated with certain optimized r and b values (marked with a dashed line). The energy-minimized relation between r and b can be solved by setting the energy derivative with respect to r to zero.

$$\frac{dE}{dr} = 0 \rightarrow b_{\mathrm{TOTAL}} = \sqrt{\frac{8\pi^2\gamma r}{\mu}\left(\frac{R^2 + r^2}{R^2 - r^2}\right)} \quad (6)$$

The first factor in Eq. 6 represents the effect from Frank's hollow-tube mechanism (see Eq. 3) (*22*), whereas the second factor is the modification due to the Eshelby-twist pathway. The Eshelby-twist component can also be expressed explicitly as the difference between Eq. 6 and Eq. 3.

$$b_{\mathrm{TWIST}} = b_{\mathrm{TOTAL}} - b_{\mathrm{TUBE}} = \sqrt{\frac{8\pi^2\gamma r}{\mu}}\left(\frac{R^2 + r^2}{R^2 - r^2} - 1\right) \quad (7)$$

This direct relation between the r and b variables along the energy valley (Eq. 6 and dashed line in Fig. 3C) contains the contributions to the total energy from the Eshelby-twist and hollow-tube components and can be alternately displayed as a plot of b versus r/R (Fig. 3D). At low b, the total energy minimization approximates the Frank hollow-tube mechanism, and most energy is relieved by making the tube hollow. However, at much larger b (and larger r), the total energy minimization begins to follow the Eshelby-twist line. That is, as the NT becomes a cylindrical shell, creating more surface becomes energetically forbidden, and most energy goes toward the Eshelby twist. For the ZnO NT in Fig. 3B, the vertical dashed line (r/R = 12.6 nm/2.9 nm = 0.23) in Fig. 3D predicts that this tube follows the former limit, and the strain energy is alleviated almost purely by hollowing out into a NT, consistent with our observation of very little Eshelby twist in ZnO NTs.

So what then is the Burgers vector magnitude (b) for these ZnO NTs? Burgers vector magnitudes are generally difficult to determine. Following scanning probe microscopy techniques that measure the growth spiral step height around the screw dislocation core as b (*24*, *30*), we suggest a measurement of the step height from the tip of NTs using high-resolution TEM (HRTEM) (Fig. 3B and fig. S7). Because LBL growth is expected to be virtually shut off under these conditions, this step edge is unlikely the result of a nucleated island. For NTs that show clear c-axis planes, the distance between the highest lattice fringe and the last lattice fringe that is continuous throughout the NT can be approximated as b, which is about 1.9 nm for this representative NT (Fig. 3B). Alternatively, from dislocation energy minimization (Eq. 6) we can directly estimate the b to be 1.4 nm for the same NT (R = 12.6 nm and r = 2.9 nm). Despite the limitations of both approximations, they give similar estimates.

To prove that the growth of ZnO NWs, NTs, and thicker NRs containing axial screw dislocations (for evidence of axial dislocations in NRs, see fig. S11) is driven by dislocations, we compare experimentally determined growth kinetics with those predicted using fundamental BCF (*10*, *11*) and LBL crystal growth theories (*10*). Thorough treatment of both crystal growth theories in detail can be found in the supporting online material (*20*). Briefly, BCF theory predicts a dislocation-growth rate ($R_{\mathrm{dislocation}}$) linearly dependent on supersaturation

$$R_{\mathrm{dislocation}} = C\sigma \quad (8)$$

where the rate constant C can be calculated (*10*, *11*, *20*). In contrast, LBL growth has an exponential growth rate (R_{lbl})

$$R_{\mathrm{lbl}} = J_{\mathrm{o}}L^2\beta \propto e^{\left(-\frac{g_n}{kT}\right)}L^2\beta \quad (9)$$

where J_{o} is the rate of 2D nucleation, L is the length of the facet (assuming a square growth facet), β is the step height, k is Boltzmanns constant, T is the temperature, and g_n is the energy barrier to 2D nucleation, which is inversely proportional to supersaturation (*20*). These expressions illustrate that, although LBL growth requires the formation of 2D nuclei by overcoming the energy barrier g_n, dislocation growth has no such barrier because of self-perpetuating growth steps; therefore, at low supersaturations dislocation growth dominates. Only at supersaturations above the critical supersaturation of forming 2D nuclei is LBL expected to overtake dislocation growth (fig. S1). These macroscopic growth rates for dislocation (Eq. 8) and LBL (Eq. 9) growth are plotted as a function of supersaturation for ZnO growth using appropriate parameters (Fig. 4) (*20*).

We have determined experimental axial growth rates by conducting a series of growth experiments over a range of precursor concentrations (c) from 20 μM to 10 mM and surveying the lengths of the NR/NW/NT products (fig. S9) (*20*). These experimental growth rates are plotted as a function of supersaturation (σ) against those theoretically predicted (Fig. 4). To convert c to σ using Eq. 1, we empirically determine the equilibrium concentration (c_0) to be 11 μM by finding the concentration at which the initial ZnO seed crystals are stable, that is, neither dissolving nor growing into NWs (fig. S8) (*20*). It is clear that the experimentally measured ZnO NR/NW/NT growth rates follow the rate law predicted by dislocation-driven growth and not that predicted by LBL growth. Because a single value of specific surface energy for ZnO, which heavily influences g_n, has not been reported, LBL growth rates calculated using a conservative value of 0.16 J/m^2 and an intermediate value of 0.31 J/m^2 (among the reported surface energy range of 0.1 to 0.7 J/m^2) are displayed in Fig. 4. For all calculations, experimental growth rates do not follow the LBL model. Although the apparent good match between experimental and theoretical dislocation growth rates might be incidental, the logarithmic growth rate plot (inset of Fig. 4) shows that the dislocation and LBL growth rate trends are so different that even errors of several orders of magnitude would not support a different conclusion. Together with the observation of axial dislocations and NT formation, this proves that the solution growth of ZnO NRs, NWs, and NTs in various concentration regimes, observed by us or reported in the literature, is indeed driven by dislocations. Furthermore, the observed decrease in aspect ratio with increasing supersaturation (Fig. 1, C to A) may be explained by the competition between dislocation and LBL growth mechanisms at different supersaturations (fig. S10) (*20*). Because only axial dislocations are observed, LBL growth accounts for radial growth (broadening) exclusively, and the barrier to 2D nucleation on the side walls heavily impacts aspect ratio. Supersaturations below this barrier yield high-aspect-ratio NWs/NTs; those above it do not (fig. S10, C and D).

We have shown that large axial screw dislocations in NWs result in the spontaneous formation of single-crystal NTs as the equilibrium morphology and explained why thick-walled dislocated NTs have very little Eshelby twist. The growth kinetics of these materials follow the prediction of the dislocation growth mechanism as described by BCF theory, confirming that axial screw dislocations seen in these materials drive the anisotropic growth of NWs or NTs. The connections between supersaturation, preferred crystal growth mechanism, energetics of dislocations, and the final morphology elucidated here present unifying concepts to explain and control the variety of 1D nanomaterial morphologies (NR, NW, and NT) reported. Although ZnO is used as a specific example herein, we provide a general theoretical framework for controlling solution NW/NT growth that can be applied to other materials.

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Supporting Online Material
www.sciencemag.org/cgi/content/full/328/5977/476/DC1
Materials and Methods
Figs. S1 to S11
Table S1
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Monolithic Carbide-Derived Carbon Films for Micro-Supercapacitors

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Microbatteries with dimensions of tens to hundreds of micrometers that are produced by common microfabrication techniques are poised to provide integration of power sources onto electronic devices, but they still suffer from poor cycle lifetime, as well as power and temperature range of operation issues that are alleviated with the use of supercapacitors. There have been a few reports on thin-film and other micro-supercapacitors, but they are either too thin to provide sufficient energy or the technology is not scalable. By etching supercapacitor electrodes into conductive titanium carbide substrates, we demonstrate that monolithic carbon films lead to a volumetric capacity exceeding that of micro- and macroscale supercapacitors reported thus far, by a factor of 2. This study also provides the framework for integration of high-performance micro-supercapacitors onto a variety of devices.

Microbatteries with the capability to be fabricated with length scales controlled in the micrometer range improve performance over their larger cousins by decreasing diffusion lengths, increasing the fraction of electroactive materials and making use of precise fabrication protocols. The prospect of integrating microbatteries as discrete power sources with the micro-electromechanical systems (MEMS), the devices they power, and the capacity for autonomous recharging represents a conceptual leap forward over existing methods for powering devices. This could potentially increase the density of devices allowing improved functionality, reduced complexity, and enhanced redundancy by removing intricate interconnects to bulk-sized batteries. Currently, advanced rechargeable microbatteries that use thin-film technologies are commercially available (*1*), but they suffer from many of the limitations of their larger counterparts, namely limited cycle life, abrupt failure, poor low-temperature kinetics, and safety concerns associated with using lithium (*2*). Even three-dimensional (3D) batteries (*1*), which are expected to overcome power limitations by further shortening electrolyte path lengths, cannot avoid fast failure because of the inevitable self-discharge caused by electron tunneling through marginally conductive thin dielectric coatings (solid electrolytes) and repeated recharging cycles. Electrochemical capacitors (ECs), also called ultracapacitors or supercapacitors, can solve these lifetime and power issues and provide a bridge between devices operating with short charge-discharge times (<0.1 s) and longer discharge times (>0.1 hours) under and over which dielectric or electrolytic capacitors and batteries, respectively, find their niche (*3*). However, compared to lithium-ion batteries, very little work has been done to integrate ECs on a chip or to produce thin- and thick-film ECs in general.

The power density and cycle time of ECs enable them to improve the efficiency of a battery when the two are used together (*4*). ECs can harvest the excess kinetic energy, such as in the braking of a motor vehicle or the vibrations of a moving object. ECs store energy through reversible ion adsorption at the surface of high specific surface area carbons at the carbon-electrolyte interface, in a so-called double-layer (*3*), whereas batteries store electrical energy in chemical bonds in a bulk material (*5*, *6*). ECs do not require slow charge or discharge to satisfy relatively sluggish electrochemical charge-transfer kinetics that maintain the thermodynamic steady state in batteries. Additionally, because only physical motion of charge carriers dictates the charge stored (*7*), they can handle currents that are larger by several orders of magnitude (*8*). Moreover, because EC electrostatics avoids battery and fuel-cell chemical kinetics, EC efficiency and reversibility exceed 90%, even at very high discharge rates (*4*). In combination with a practically infinite cycle life, ECs seem ideal for capturing and storing energy from renewable resources and for on-chip operation.

There have been notable advances in the micro-supercapacitor field, which were mostly focused on increasing micro-supercapacitor energy density by using different active materials (*9*) and designs, such as carbon nanotubes (CNTs) (*10*, *11*), activated carbons (*12*), polymers (*13*),

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and metal oxides (*13*, *14*). CNT films were used in 2D thin-film micro-supercapacitors with several square centimeter footprints; the "micro-" prefix referring here to the film thickness (about 10 μm thick) (*10*, *15*). The films gave respectable gravimetric and volumetric capacitance, but the functional capacitance per unit area of device was low (*10*). Activated carbon powders have a better performance in terms of energy per unit area (*12*), but they need to be processed into films before use, and this limits their interest for microdevice fabrication. Conducting polymers have shown fairly good performance (*13*, *16*), but are not yet compatible with standard microfabrication protocols. Oxide-based thin-film ECs have shown high performance, approaching the theoretical limit for capacitance (for example, 1000 F/g for MnO_2) (*17*, *18*). However, the poor electrical conductivity and high impedances associated with surface intercalation redox reactions of these oxides have limited practical film thicknesses to a few microns. Nanotubes have been added to the films to increase the electrical conductivity, but the complexity of manufacturing limits practical applications of such composite electrodes.

Carbide-derived carbon (CDC) is a class of carbon materials produced by selectively etching metals from metal carbides using chlorine at elevated temperatures in a process that is similar to current dry-etching techniques for MEMS and microchip fabrication. CDC has been shown to have excellent performance as the active material in traditionally processed ECs (*19*), because it can have its microstructure precisely tuned by tailoring the synthesis conditions for a particular electrolyte (*20*). In the realm of microfabricated supercapacitors, CDC is attractive for two reasons: First, the precursor carbides are conductive and can be deposited in uniform thin and thick films by well-known chemical and physical vapor deposition (CVD and PVD, respectively) techniques (*21*). Then the chlorination process can be performed at temperatures at least as low as 200°C (*22*), and the resulting coatings are well-adhered with an atomically perfect interface (*23*), which minimizes device impedance. This technology can be used to produce the microfabricated ECs on the same chip as the integrated circuits, which they are powering, as schematically shown in Fig. 1. Chlorine-containing plasma etching of materials in semiconductor manufacturing is a well-established technique and is similar to the chlorination procedure in CDC manufacturing. Continuous porous carbon films cannot be produced by conventional CVD, PVD, or other techniques, and the high-temperature activation needed to produce the microstructures necessary for supercapacitor performance in CVD carbons would destroy the devices they were intended to power.

As a first step toward integrated energy-storage devices, thin CDC films were produced on bulk TiC ceramic plates. The electrochemical behavior was studied in two common EC electrolytes, aqueous sulfuric acid and tetraethylammonium tetrafluoroborate ($TEABF_4$) in acetonitrile.

This approach also allows for the study of carbons without interparticle porosity, which could potentially decrease the diffusion length and increase the number of ions available for charge storage in a unit volume. It could also aid in generating an understanding of the diffusion limi-

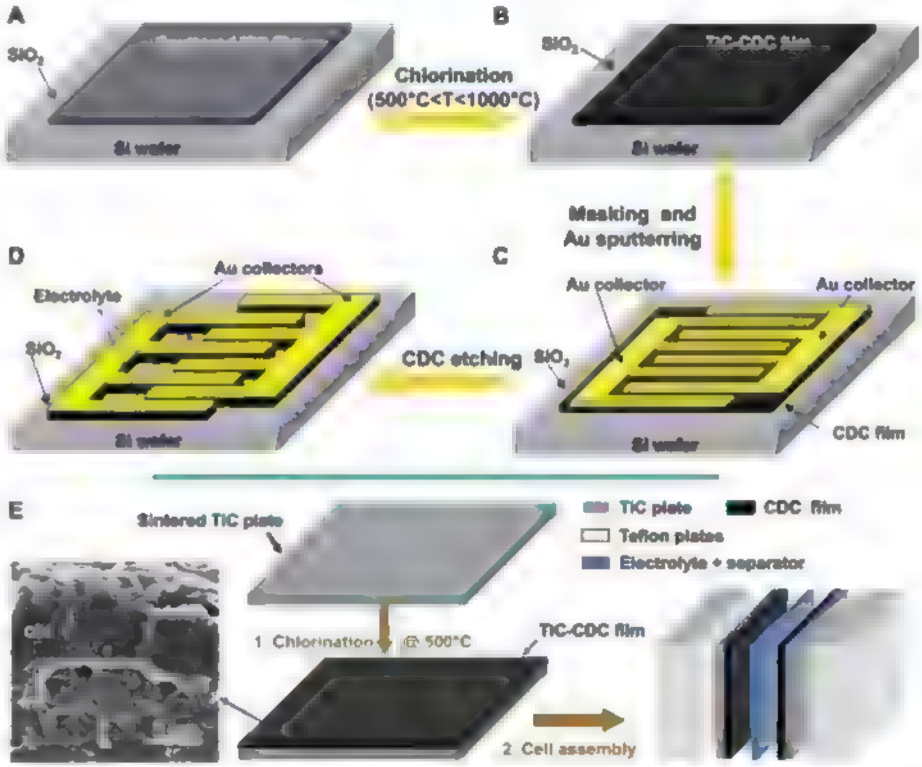

Fig. 1. (**A** to **D**) Schematic of the fabrication of a micro-supercapacitor integrated onto a silicon chip based on the bulk CDC film process. Standard photolithography techniques can be used for fabricating CDC capacitor electrodes (oxidative etching in oxygen plasma) and deposition of gold current collectors. (**E**) CDC synthesis and electrochemical test cell preparation schematic. Ti is extracted from TiC as $TiCl_4$, forming a porous carbon film. Two TiC plates with the same CDC coating thickness ranging from 1 to 200 μm are placed face to face and separated by a polymer fabric soaked with the electrolyte. SEM micrograph shows a representative image of a CDC/TiC interface, with a good film adhesion and a glassy film fracture surface typical of amorphous carbon.

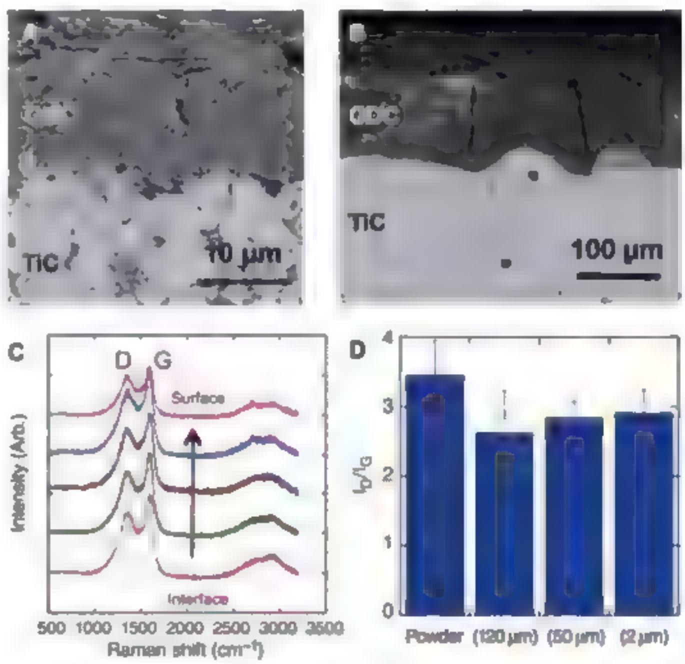

Fig. 2. CDC films on TiC. (**A**) Backscattered electron image showing a uniform carbon film and a strong TiC/CDC interface on a sample chlorinated for about 1 min. (**B**) Backscattered electron image showing a thick carbon film (5-min chlorination, ~100-μm film) with good adhesion, in spite of some microcracking. (**C**) Raman spectra show no major change in the structure of the film from the carbon-TiC interface to the surface of a ~50-μm film. Arb, arbitrary units. (**D**) Comparison of intensity ratios of D and G bands of graphitic carbon shows that there is little difference in the carbon structure of the films with the thickness ranging from 2 to 120 μm.

tations that may exist in thicker films when transport porosity in the form of interstitial voids between carbon particles in traditionally processed electrodes is removed. Likewise, as the electrolyte density is larger than the bulk density of activated carbon, monolithic porous films without interparticle porosity should show improved overall performance simply due to elimination of excess electrolytes located in macropores.

Sintered TiC ceramic plates (Angstrom Sciences, Duquesne, PA, purity > 99.5%, density = 4.93 g/cm^3) were cut to size and polished to be as thin as practically feasible (~300 μm) to minimize resistance before being chlorinated on one face for times ranging from 15 s to 5 min, which led to coatings from ~2 to ~200 μm. Scanning electron microscopy (SEM) images of ~5-μm (Fig. 1E), ~10-μm (Fig. 2A), and ~100-μm (Fig. 2B) films show a fairly uniform thickness and good adherence to the underlying TiC; similar results were obtained with all the samples. The film thickness for each sample was measured with the use of SEM. 500°C was chosen as the chlorination temperature because, at lower synthesis temperatures, the pore size has been shown to be too small for effective storage of tetraethylammonium cations (*24*), and at synthesis temperatures higher than this, the chlorination kinetics are too fast to have good control over coating thickness.

SEM micrographs of the film surface (Fig. 2, A and B) show some microcracking due to tensile stresses that develop in the film after Ti removal. The amount of microcracking increases with increasing coating thickness, but the cracks stay confined in the surface layer. The plates retain their shape and do not fall apart, even after complete transformation to carbon, and the microcracking that has already occurred did not lead to CDC film delamination from the TiC substrate. Raman spectroscopy of the coating surface for three different coating thicknesses (Fig. 2C) shows that the intensity ratio of disorder-induced (D) and graphite (G) bands of carbon (I_D/I_G) slightly decreases with increasing coating thickness, indicating a possible increase in microstructural ordering for thicker films at the surface. This is in line with SEM observations showing increasing relaxation of stresses at the surface. A longer time at elevated temperatures during the synthesis for thicker films leads to somewhat higher levels of ordering.

Raman microspectroscopy of a ~50-μm film (Fig. 2C) showed a fairly uniform I_D/I_G ratio throughout the coating thickness. At the film surface, there seems to be a slightly larger amount of ordering, but in general, the coatings are all of very similar microstructure. This increased ordering at the surface is probably related to the microcracking. The fact that Raman spectra (collected from the surface of coatings with different thickness and throughout the thickness of a 50-μm coating) are fairly consistent leads us to believe that the carbon is of very similar microstructure and porosity. The gas sorption isotherms of bulk CDC plates were similar to those of powders and, although precise sorption measurements on thin CDC films were impossible, we anticipate that the pore size of the samples was very close to 0.7 nm, as measured on TiC-CDC powders synthesized at 500°C (*24*).

Electrochemical measurements of CDC films were carried out in a three-electrode configuration with a large overcapacitive activated carbon counter-electrode in both 1 M $TEABF_4$ and 1 M H_2SO_4, as well as two-electrode cells with symmetric bulk CDC film electrodes (see the supporting online material for details). Three-electrode cells were used to evaluate Faradaic processes that may be present and the available potential window, and two-electrode cells were constructed to simulate actual device behavior. These electrolytes were chosen because they represent the most widely studied aqueous and organic electrolytes and are the most commercially used. Cyclic voltammograms (CVs) for 50-μm traditionally processed 500°C TiC-CDC powder electrodes are also included for direct comparison. Both CVs of CDC films show good non-Faradaic response, with voltage windows similar to powder electrodes (Fig. 3). If there were a substantial amount of impurities due to chlorine and chlorides being trapped in the film, there would be Faradaic currents, especially at the extents of cycling. In H_2SO_4 (Fig. 3B), there are minor current peaks at both of the switching potentials, the origin of which needs to be studied further; the peaks, however, decrease with cycling. The shape of the CV is different for the forward sweep and backward sweep, which shows the importance of pore accessibility, desolvation, and effective ion sizes (*24*, *25*). Recent studies have shown that the TEA^+ cation may have difficulties entering very small pores because of its larger size relative to BF_4^-, hence the slower saturation for the negative scan and an asymmetric behavior (*26*, *27*). Accordingly, the tetraethylammonium cation adsorption drives the electrochemical behavior at high cell voltage.

Volumetric capacitance was calculated for each of the different film thicknesses (Fig. 4). For both $TEABF_4$ and H_2SO_4, the volumetric capacitance decreases with increasing coating thickness. This is especially pronounced in the organic electrolyte, where there is a huge increase in volumetric capacitance as the film thickness decreases from 200 to ~2 μm. For a CDC film of ~50 μm in $TEABF_4$, the volumetric capacitance (~60 F/cm^3) is similar to what was observed in a ~300-μm traditionally processed electrode from carbon powders (~50 F/cm^3) (*25*). Likewise, in 1M H_2SO_4 electrolyte, for films thicker than ~100 μm, the

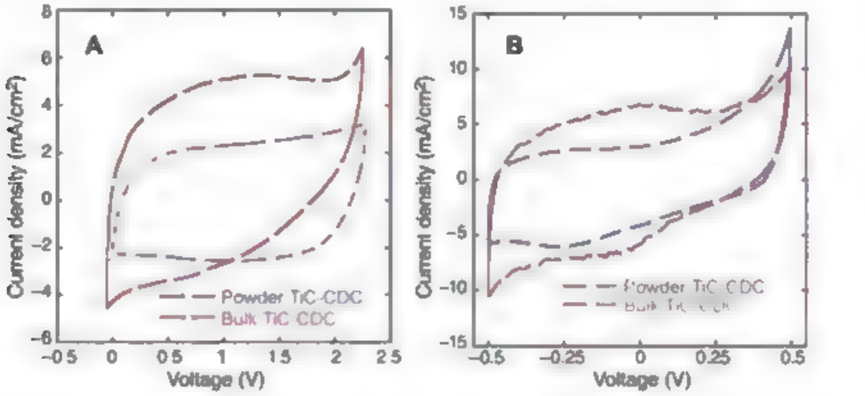

Fig. 3. Cyclic voltammetry data for CDC films in two-electrode cells. **(A)** A ~50-μm film and a ~50-μm traditional powder electrode in $TEABF_4$. **(B)** A ~50-μm film and a ~50-μm traditional powder electrode in H_2SO_4. Monolithic CDC shows a larger capacitance compared with powder electrodes even in fairly thick films.

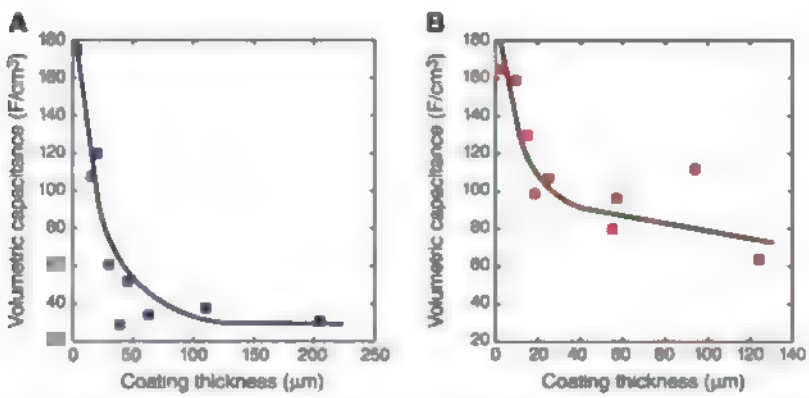

Fig. 4. Volumetric capacitance as a function of the film thickness in **(A)** $TEABF_4$ and **(B)** H_2SO_4. In the case of aqueous electrolytes, films with a thickness of up to 100 μm provide outstanding volumetric capacitance. In the case of an organic electrolyte, we believe that a larger size and lower mobility of the TEA ion is responsible for lower capacitance values for films thicker than 20 μm.

volumetric capacitance is similar to what was measured on a ~300-μm-thick traditionally processed electrode (~80 F/cm^3).

As the coating thickness decreases to ~2 μm, the volumetric capacitance increases to nearly 180 F/cm^3 in $TEABF_4$ electrolyte and ~160 F/cm^3 in 1M H_2SO_4. The spacing between cracks is larger than the film thickness (Fig. 3B); thus, electrolyte transport is controlled by the transport from bulk electrolyte to the current collector through the entire film thickness, making crack influence on capacitance marginal at best. Also, the crack volume in comparison with the pore volume of the CDC layer (>50%) does not lead to a substantial increase in electrolyte volume or electrode surface area (<1%). Simply removing ~50% of empty volume between particles in traditional electrodes would provide volumetric capacitance numbers of ~100 F/cm^3 in organic electrolyte and ~160 F/cm^3 in sulfuric acid electrolyte; it is believed that this is the major reason for the thin-film results. The extremely intimate contact between the underlying current collector and CDC film would also facilitate good electron transfer into the film, limiting the voltage drop through this interface and resulting in higher charge compensation in the double-layer, which could explain capacitance values above what is expected based solely on sphere-packing assumptions. The decrease in capacitance with thicker films is most likely due to microstructural rearrangement from surface stresses relaxing, which results in porosity collapse and perturbation of the interconnected structure that facilitates electron conduction. The effects of electrolyte starvation with thicker films coupled to structure collapse may also play a role in the drop in capacitance values [as previously shown by Zheng *et al.* (*28*)], with thicker films requiring a larger number of ions to migrate from the bulk electrolyte into the pore structure.

Although we observed microcracking in the TiC-CDC films in this study, it has previously been shown that dense coatings can be made to 200-μm thickness for SiC-CDC films (*29*). Earlier work chlorinating sputtered amorphous TiC, which is the simplest method for patterning carbide substrates for micro-supercapacitors on devices, has shown that TiC-CDC can also be produced crack-free, at least in the form of 0.5-μm films (*21*). Therefore, in terms of extrapolating these results to realizable micro-supercapacitors, we expect that what may be viewed as technological hurdles should, in fact, lead to better-functioning devices.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/328/5977/480/DC1
Materials and Methods
Fig. S1

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Constraints on the Formation Age of Cometary Material from the NASA Stardust Mission

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We measured the ^{26}Al-^{26}Mg isotope systematics of a ~5-micrometer refractory particle, Coki, returned from comet 81P/Wild 2 in order to relate the time scales of formation of cometary inclusions to their meteoritic counterparts. The data show no evidence of radiogenic ^{26}Mg and define an upper limit to the abundance of ^{26}Al at the time of particle formation: $^{26}Al/^{27}Al < 1 \times 10^{-5}$. The absence of ^{26}Al indicates that Coki formed >1.7 million years after the oldest solids in the solar system, calcium- and aluminum-rich inclusions (CAIs). The data suggest that high-temperature inner solar system material formed, was subsequently transferred to the Kuiper Belt, and was incorporated into comets several million years after CAI formation.

The Stardust mission to comet 81P/Wild 2 was designed around the premise that comets preserve pristine remnants of the material from which the solar system formed; in 2006, Stardust returned the first samples from a comet. The mission was expected to provide a unique window into the early solar system by returning a mix of solar system condensates, amorphous grains from the interstellar medium, and true stardust (crystalline grains originating in distant stars). Initial results, however, indicate that Wild 2 instead contains an abundance of high-temperature silicate and oxide minerals analogous to minerals in carbonaceous chondrites (*1*–*5*). The detection of Wild 2 particles that resemble calcium- and aluminum-rich inclusions (CAIs) (*6*) is particularly noteworthy because CAIs were most plausibly created within 1 AU of the infant Sun (*7*) and are the oldest objects formed in the solar nebula (*8*). The presence of inner solar system material in Wild 2 (*1*–*3*, *9*) underscores the importance of radial transport of material

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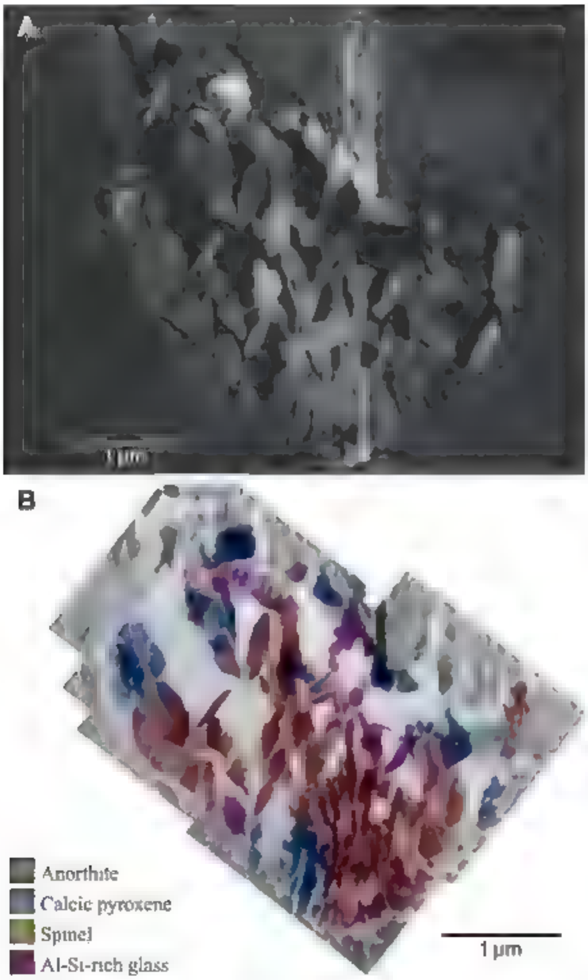

Fig. 1. **(A)** Secondary electron image of the Coki section analyzed in this study, showing mineral shards surrounded by compressed aerogel. **(B)** Corresponding false-color mineral map overlaid on a montage of bright-field TEM images (*13*).

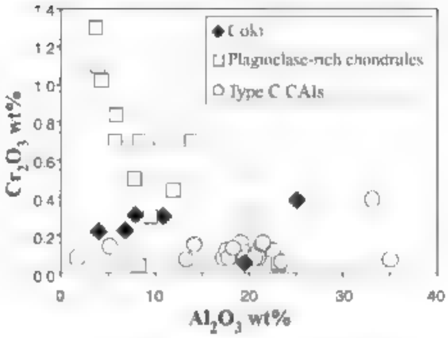

Fig. 2. Coki pyroxene chemical compositions as compared to type C CAIs (*15*, *16*) and plagioclase-rich chondrules (*14*, *16*, *33*).

Table 1. ^{26}Al-^{26}Mg isotopic data from Coki. Uncertainties are two standard deviations.

Sample	$^{27}Al/^{24}Mg$	$\delta^{26}Mg$ (‰)*
Coki 1†	342 ± 34	−17 ± 37
Coki 2‡	150 ± 15	18 ± 45
Coki 3§	6.9 ± 0.7	1.6 ± 6.5

*Per mil deviation in $^{26}Mg/^{24}Mg$ relative to terrestrial Mg after correction for mass-dependent fractionation. See (*13*) for details. †Includes pixels with $^{27}Al/^{24}Mg$ > 200. ‡Includes pixels with $^{27}Al/^{24}Mg$ between 100 and 200. §Includes pixels with $^{27}Al/^{24}Mg$ < 10.

over large distances in the early solar nebula, and it raises key questions regarding the time scale of formation of comets and the relationship between Wild 2 and other primitive solar nebula objects.

With a half-life of 730,000 years, the decay of the short-lived radionuclide ^{26}Al to ^{26}Mg provides a high-resolution relative chronometer for events occurring during the first several million years of solar system history. Assuming a homogeneous initial distribution of ^{26}Al within the solar nebula (*10*), differences in the inferred initial $^{26}Al/^{27}Al$ can be ascribed to the passage of time. Most CAIs contain radiogenic ^{26}Mg as a result of the in situ decay of ^{26}Al (*10*). CAIs that contain little to no radiogenic ^{26}Mg fall primarily into two categories: (i) highly refractory grains [e.g., (*11*)] and rare FUN inclusions named for their fractionation and unidentified nuclear isotopic effects, which are believed to have formed very early (*12*); and (ii) CAIs that show clear petrographic evidence for later reprocessing (*10*).

We applied the ^{26}Al-^{26}Mg isotope system to a recently discovered refractory particle from Wild 2 (C2061,3,141,0,0; hereafter Coki). Coki contains no detectable radiogenic ^{26}Mg, strongly suggestive of late formation at least 1.7 million years after most CAIs. The ^{26}Al-^{26}Mg data from Coki provide an important constraint on the accretion time scale of comets such as Wild 2 and the timing of radial mixing of thermally processed, high-temperature materials from the inner solar system to the outer reaches of the solar nebula.

Coki is a polycrystalline refractory particle ~5 µm in diameter, likely a fragment of a once much larger particle (*13*); it is composed mostly of anorthite with minor calcic pyroxene and an Al-Si-rich glass occurring around the edge of the particle (Fig. 1). The glass may be due to melting experienced by the particle during capture into the Stardust silica aerogel collector. Small (<200 nm) spinel crystals are enclosed in glass and anorthite. The abundance of anorthite and absence of melilite (either within the Coki particle or anywhere along its deceleration track) suggest that Coki most closely resembles a minor class of CAIs (type C) or plagioclase-rich chondrules (*6*, *14*, *15*). Coki pyroxene compositions are Ti-rich and Fe- and Cr-poor (Fig. 2, fig. S1, and table S1) relative to pyroxene commonly found in plagioclase-rich chondrules [e.g., (*14*)], which suggests that Coki may be most comparable to type C CAIs. Both type C CAIs and plagioclase-rich chondrules show clear petrographic evidence for complex multistage histories, including melting of refractory precursor materials and assimilation of late-stage metamorphic minerals in the chondrite-forming region (*6*, *14*–*16*).

We used a secondary ion mass spectrometer with nanometer-scale spatial resolution, the Cameca NanoSIMS 50, to measure the Mg isotope composition of Coki anorthite. An electron-transparent section, ~3 µm in diameter and 0.1 µm thick, was first mapped by transmission electron microscopy energy-dispersive spectroscopy (TEM/EDS) (*13*) (Fig. 1). The section was then prepared for NanoSIMS analysis with the use of a focused ion beam instrument to deposit a Pt support film behind the Coki section and to remove interfering Mg-rich minerals (*13*). We simultaneously collected four ion images corresponding to $^{24}Mg^+$, $^{25}Mg^+$, $^{26}Mg^+$, and $^{27}Al^+$ secondary ions. The ion images were subdivided into three spatially continuous regions on the basis of $^{27}Al/^{24}Mg$ ratio, and Mg isotope ratios were calculated by summing the total ion intensity of each isotope over each region (*13*) (Table 1).

The Mg isotope composition of Coki anorthite is indistinguishable from that of the terrestrial plagioclase standards. We found no evidence in Coki for either radiogenic ^{26}Mg from the decay of ^{26}Al or mass-dependent fractionation of Mg isotopes (Table 1 and Fig. 3). The upper limit for the initial abundance of ^{26}Al at the time Coki crystallized is $^{26}Al/^{27}Al < 1 \times 10^{-5}$, according to the 2σ upper bound to the slope of a line fitted to the data. The absence of substantial mass-dependent fractionation of Mg isotopes indicates that Coki is not a member of the rare group of CAIs known as FUN inclusions (*12*).

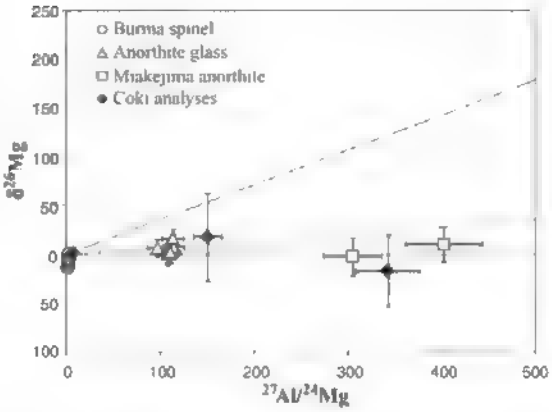

Fig. 3. ^{26}Al-^{26}Mg evolution diagram for Coki. The solid horizontal line corresponds to terrestrial Mg. The dashed line indicates the canonical ^{26}Al/^{27}Al value of 5×10^{-5}; the dotted line represents the 2σ upper error bound on a line fitted to the data and forced through the origin corresponding to initial ^{26}Al/^{27}Al $< 1 \times 10^{-5}$.

The ^{26}Al-^{26}Mg isotope systematics of primitive solar system materials establish a framework for the interpretation of the Coki Al-Mg data. The initial abundance of ^{26}Al in CAIs provides the anchor point for the ^{26}Al-^{26}Mg chronometer; the ^{26}Al-^{26}Mg record of CAIs and chondrules is best explained by formation in an isotopically homogeneous nebular reservoir characterized by an initial ^{26}Al/^{27}Al ratio of $\sim 5 \times 10^{-5}$ (*10*). Recent high-precision studies of ^{26}Al in CAIs (*17*, *18*) and chondrules (*19*) support the inference of a uniform initial distribution of ^{26}Al/^{27}Al in the solar nebula and a very short time interval (<20,000 years) for the primary crystallization of CAIs. Type C CAIs and chondrules, with initial ^{26}Al/^{27}Al ratios of $\ll 5 \times 10^{-5}$, typically show textural and mineralogical evidence for extensive melting of precursor materials [e.g., (*20*)], consistent with the absence of ^{26}Al. The ^{26}Al-^{26}Mg record of plagioclase-rich chondrules indicates that the time interval between CAI formation and the onset of chondrule formation is ~1 million years (*21*, *22*) and that transient events capable of producing high-temperature nebular components in the inner solar system persisted for close to 4 million years (*23*–*25*).

Our determination that Coki formed with an initial ^{26}Al/^{27}Al of $< 1 \times 10^{-5}$ indicates that Coki crystallized at least 1.7 million years after the onset of CAI formation. This value is consistent with data for type C CAIs and plagioclase-rich chondrules that typically yield initial ^{26}Al/^{27}Al $\leq 1 \times 10^{-5}$ [(*23*) and references therein; (*26*)]. The lack of ^{26}Al in some highly refractory phases [e.g., hibonite (*11*)] has been interpreted as very early formation prior to the incorporation or homogenization of ^{26}Al in the accretion disk. However, the petrography and mineral composition of Coki are inconsistent with formation as very early condensates. The lack of ^{26}Al in Coki is also unlikely to be attributable to later redistribution of radiogenic ^{26}Mg either on Wild 2 or during capture in aerogel. The poorly consolidated and fine-grained nature of the material collected from Wild 2 indicates that it had not been lithified and altered in Wild 2 by internal processes such as heating, compaction, or aqueous alteration (*3*). Although all particles were modified to some degree by capture in aerogel, particles that are larger than 1 μm, such as Coki, are typically well preserved and appear to have been protected by their own thermal inertia (*3*). We estimate that the distance over which Mg diffused in anorthite [using the diffusion coefficient of (*27*)] during the conditions of capture in aerogel [i.e., $T \approx 2000$ K, $t > 1$ μs (*3*)] is less than 1 nm.

We postulate that Coki formed by melting of solid precursor materials during transient high-temperature events in the inner solar system, analogous to the formation of type C CAIs and chondrules (*20*, *28*). The chemical and isotopic data suggest that Coki is transitional between the only other CAI-like particle described from Wild 2, named Inti (*1*, *3*, *9*), and the chondrule-like objects from Wild 2 described by Nakamura *et al.* (*2*). As such, Coki may provide a direct link between primary CAI formation and later chondrule formation. Inti closely resembles type B CAIs in its mineralogy and ^{16}O-rich isotope composition (*1*, *9*), whereas the ferromagnesian chondrule-like objects have less refractory chemical compositions and display a range of O-isotope compositions suggesting that they experienced oxygen isotope exchange in a ^{16}O-depleted reservoir (*2*). These observations lead to the conclusion made in previous studies (*1*–*4*) that Wild 2 contains an abundance of chemically and thermally processed high-temperature material from the inner solar system. In this sense, Wild 2 is analogous to carbonaceous chondrite meteorites (*5*).

As an additional member of the collection of refractory materials from Wild 2, Coki adds weight to the evidence suggesting that high-temperature silicate and oxide mineral assemblages formed close to the Sun and were subsequently transported to the region of comet accretion. Coki provides a temporal constraint demonstrating that refractory material supplied to the Kuiper Belt crystallized at least 1.7 million years after the onset of CAI formation. This observation in turn requires transport of inner solar system material to the outer reaches of the solar system at distances exceeding 30 AU and incorporation into cometary bodies over an extended period of at least several million years. Outward transport of Coki to the Kuiper Belt must have occurred as late as (if not later than) the time over which chondritic meteorites and the oldest differentiated meteorites formed [see (*29*)]. The age constraint derived from Coki indicates that the transport mechanisms that supplied high-temperature inner solar system material to the outer reaches of the solar nebula—whether by lofting above the disk in an X-wind model (*30*) or via mixing processes within the solar nebula [e.g., (*31*, *32*)]—operated over a time scale of >2 million years as solids settled to the midplane and the disk evolved.

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Asian Monsoon Failure and Megadrought During the Last Millennium

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The Asian monsoon system affects more than half of humanity worldwide, yet the dynamical processes that govern its complex spatiotemporal variability are not sufficiently understood to model and predict its behavior, due in part to inadequate long-term climate observations. Here we present the Monsoon Asia Drought Atlas (MADA), a seasonally resolved gridded spatial reconstruction of Asian monsoon drought and pluvials over the past millennium, derived from a network of tree-ring chronologies. MADA provides the spatiotemporal details of known historic monsoon failures and reveals the occurrence, severity, and fingerprint of previously unknown monsoon megadroughts and their close linkages to large-scale patterns of tropical Indo-Pacific sea surface temperatures. MADA thus provides a long-term context for recent monsoon variability that is critically needed for climate modeling, prediction, and attribution.

Monsoon failures, megadroughts, and extreme flooding events have repeatedly affected the agrarian peoples of Asia over the past millennium. Despite its critical importance to human populations and ecosystems, not enough is known about the long-term spatiotemporal variability of the Asian monsoon to explain the complex mechanisms that drive its variability. A scarcity of long-term instrumental climate data for many remote regions of Monsoon Asia (*1*) (fig. S1) impedes progress toward resolving these issues. In addition, global climate models fail to accurately simulate the Asian monsoon (*2*) and related tropical Indo-Pacific forcings (*3*), and these limitations have hampered our ability to plan for future, potentially rapid and nonlinear, hydroclimatic shifts in a warming world. Under such warming, Monsoon Asia appears to be particularly vulnerable (*4*, *5*).

To better elucidate the spatial complexity of the Asian monsoon (Fig. 1A), a large-scale, spatially explicit, long-term data set is needed. Such a long-term perspective is essential both for validation of climate models and for integration and comparison with other proxy, historical, and archaeological data. This context is provided here by our Monsoon Asia Drought Atlas (MADA), which offers an absolutely dated, annually resolved reconstruction of Asian monsoon spatiotemporal variability over the past thousand years. The MADA provides a seasonal- to centennial-scale window into the Asian monsoon's repeated tendency for extended dry and wet extremes with distinct spatial flavors of response—for example, to the El Niño–Southern Oscillation (ENSO) and to Pacific Decadal Variability (*6*, *7*).

Proxy records have been produced for the past millennium for regions of Monsoon Asia and the adjacent tropical Indo-Pacific from corals (*8*), ice cores (*9*), speleothems (*10*), ocean sediments (*11*), and historical data (*12*). By their nature, these records are typically restricted by their spatial and/or temporal resolution. Many cannot provide calibration and validation estimates of reconstruction skill, and/or they do not provide the detailed land area coverage needed for resolving the Asian monsoon's complex spatiotemporal variability. Here, we used tree rings from more than 300 sites across the forested areas of Monsoon Asia to reconstruct the seasonalized Palmer Drought Severity Index (PDSI) for the summer (June-July-August) monsoon season, using a well-known, gridded measure of relative drought and wetness for the globe's land areas (*1*, *13*). The gridded reconstructions that comprise the MADA are directly analogous to the

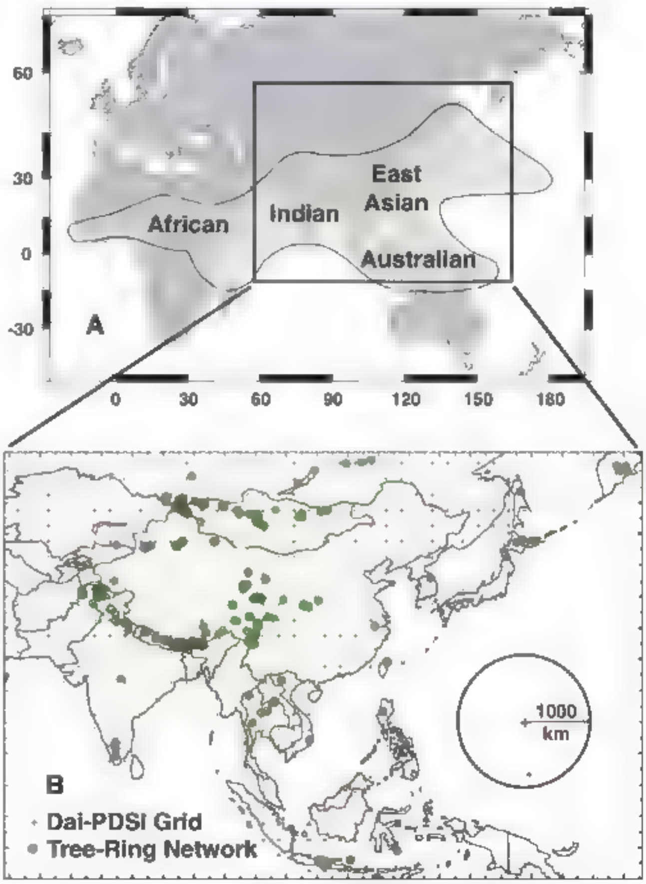

Fig. 1. **(A)** Map showing the complex regional expressions of the monsoon over Africa, India, East Asia, and south into northern Australia [redrawn from (*11*)], with the overall MADA domain enclosed by the interior black rectangle. The MADA domain limits cover all but the African portion of the greater monsoon system. **(B)** More detailed view of the MADA domain; the 534 grid points of instrumental PDSIs (*13*) (red crosses) were reconstructed by the 327-series tree-ring chronology network (*1*) (green dots). Contributors to the development of this tree-ring network are listed in table S1 (*1*).

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North American Drought Atlas (NADA) (*14*), with which it is compared below. Using this new resource, we show that monsoon failures over Asia in the modern anthropogenic period have at times been exceeded in magnitude and persistence over the past millennium, as was previously shown for megadroughts in the southwestern United States that have been linked to tropical Pacific sea surface temperature (SST) forcing (*15*).

Our Monsoon Asia reconstruction domain encompasses most of the greater Asian monsoon system (Indian, East Asian, and Australian), as well as adjacent Asian land areas to the north (Fig. 1, A and B). The 534 grid points of PDSI reconstructed for the summer monsoon season are shown in Fig. 1B, along with the network of 327 tree-ring series used for reconstruction (*1*). The latter is highly irregular relative to the PDSI grid, and its coverage is not complete because of the uneven forest cover and availability of tree species suitable for tree-ring analysis. However, using a correlation-weighted, ensemble-based modification of the "point-by-point regression" program (*1*, *14*) (figs. S5 and S6), we produced well-calibrated and validated reconstructions of summer monsoon variability over most of this domain (*1*) (fig. S7).

The MADA allows us to identify and analyze regional patterns of drought and wetness over the past millennium. This information is crucially important for identifying key modes of hydroclimatic variability that are linked to SSTs and coupled ocean/atmospheric conditions, and for providing baseline conditions for tests using climate models. Here, we used the MADA to identify the regional footprints and severity of four well-documented historical droughts: the Ming Dynasty drought (1638 to 1641) (*16*), the Strange Parallels drought (1756 to 1768) (*17*), the East India drought (1790 to 1796) (*12*), and the late Victorian Great Drought (1876 to 1878) (*18*). These comparisons also serve as validation tests of the accuracy of our reconstructed drought fields because the historical records of past drought used for comparison below are completely independent of our reconstructions and entirely predate the statistical calibration period used for reconstructing PDSI from tree rings (*1*).

The fall of the Ming Dynasty in 1644 was hastened by peasant rebellions during its final decades (*16*). Leading up to this dynastic collapse, a serious drought in the late 1630s and early 1640s appears from some historical records to have been the most severe over China for the past five centuries and may have contributed to the fall of the Ming Dynasty (*19*). Our reconstruction (Fig. 2A) shows that this drought was sharply expressed in northeastern China near Beijing, with wetter conditions prevailing toward the southeast. This pattern of reconstructed drought is similar to that of the more geographically restricted historical maps produced for the same event [figure 3 in (*19*)] and provides a more complete spatial context as compared to the historical documents.

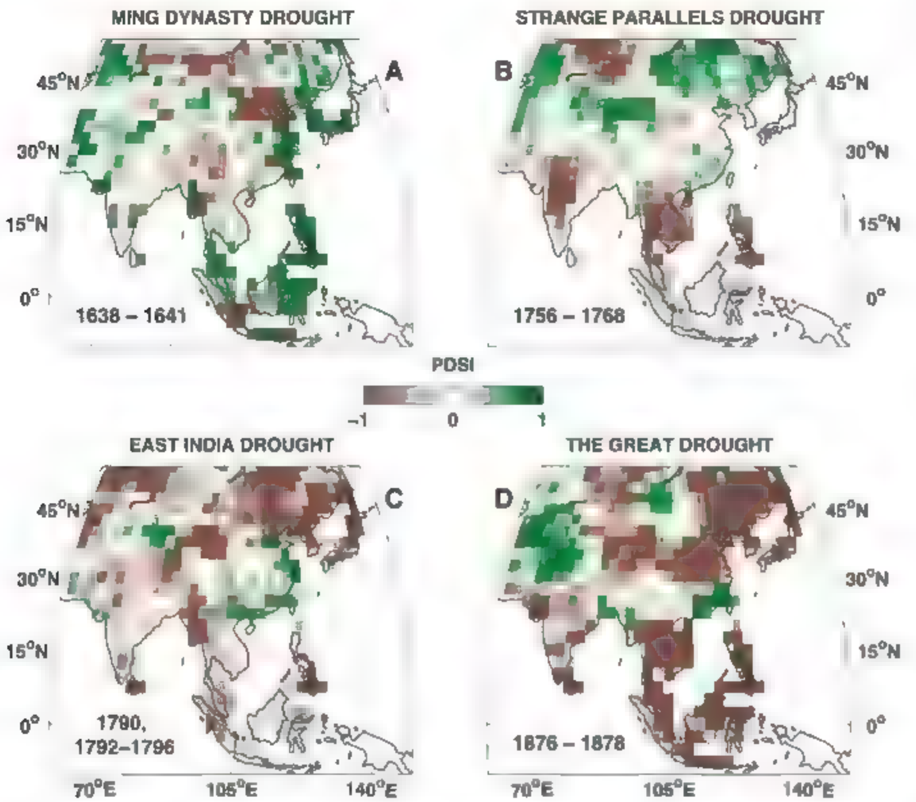

Fig. 2. Spatial drought patterns during four historical Asian droughts. Mean PDSI over each of four regional droughts identified from the historical record. (**A**) The Ming Dynasty drought (1638 to 1641) (*19*). (**B**) The Strange Parallels drought (1756 to 1768) (*17*, *20*, *21*). (**C**) The East India drought of the late 18th century (1790 and 1792 to 1796) (*12*, *22*, *23*). In 1791, much of India appears to be slightly wet, except the region around Chennai where the drought persisted (*22*). (**D**) The late Victorian Great Drought (1876 to 1878) (*18*).

The mid–18th-century Strange Parallels drought over Southeast Asia (Fig. 2B) coincided with a time of substantial societal upheaval and political reorganization across Southeast Asia and simultaneously across the Siberian plains (*17*). This drought was first identified from a teak ring-width record from northwest Thailand (*20*) and later corroborated in a northern Vietnamese cypress chronology (*21*). Our drought atlas reveals that much of India, particularly western India, was also affected by this multidecadal drought. This spatially broad and persistent "megadrought" from India to Southeast Asia is one of the most important periods of monsoon failure found in the MADA.

The East India drought (Fig. 2C) of 1790 to 1796 occurred during the great El Niño of the late 18th century, which was felt worldwide and resulted in widespread civil unrest and socioeconomic turmoil around the globe (*12*). Much has been made of this drought's effect in India, with several references to severe famine there (*12*), but the MADA does not suggest that it was any more severe over India than the other droughts highlighted here. Although this could be due to limited tree-ring coverage in India itself (Fig. 1B), the reconstructions over nearly all of the Indian subcontinent have significant validation skill (*1*) (fig. S7), and its more extreme occurrence in the southernmost part of India and near Sri Lanka (Fig. 2C) is consistent with historical data from those regions (*22*). It is therefore possible that this drought was not uniformly severe over India and that other nonclimatic factors may have contributed to the severity of the societal consequences (*12*). Indeed, the snow accumulation record from the Dasuopo ice core record (*23*) directly above northeastern India reveals a highly variable accumulation during this time. This suggests that the summer monsoon in that part of India was not uniformly weak during the East India drought. In contrast, the same ice core indicates more persistently below-average snow accumulation during the Strange Parallels drought period (*24*), consistent with our reconstruction that shows this earlier event to be more prolonged and severe. Dust and geochemical analysis of the Dasuopo record has been interpreted as evidence for severe drought in the late 18th century (*23*), but our atlas also indicates severe droughts to the west and north of the Himalayas, which could have been a source for dust accumulation at the ice core site during the winter monsoon. These observations demonstrate the utility of the MADA's full-field drought reconstruction feature for interpreting other point-based estimates of past hydroclimatic variability.

The late Victorian Great Drought of 1876 to 1878 occurred during one of the most severe El Niño events of the past 150 years (*18*). The effects of this devastating drought were felt across much of the tropics (*18*) and were particularly acute in India. A revolt against the French in Vietnam also took place as a consequence of severe drought and famine at this time, and the drought was felt as far away as Jakarta, Borneo, and New Guinea (*18*). More than 30 million people are thought to have died from famine worldwide, and Colonial-era imperialism left regional societies ill-equipped to deal with the effects of drought (*18*). Our record shows that this drought was severe across nearly all areas of Monsoon Asia and ranks as the worst of the four historical droughts shown here.

The reconstruction of historic Asian monsoon failures in full spatial detail is just one application of the MADA. Underlying these broad-scale "events" are robust long-term modes of spatiotemporal variability that can provide deeper insights into the dynamics of monsoon variability over Asia. These modes are identified here through the decomposition of the full field since 1300 C.E. into Distinct Empirical Orthogonal Functions (*25*) (DEOFs, Fig. 3). The leading DEOFs are the eigenvectors of the field rotated such that they capture the maximum variance that cannot be explained by similar decomposition of a null isotropic field conditioned on the actual data (*1*). They therefore represent a compromise between the mathematical strictures of orthogonal eigendecomposition and the local patterns produced by Varimax rotation (*1*). For this reason, DEOFs may be more readily interpretable as meaningful physical modes (*25*).

Significance testing against the null field suggests that up to five leading DEOF patterns may be interpretable in the MADA. Two of these modes are highlighted in Fig. 3, with the remaining ones shown and interpreted in (*1*) (fig. S8). The leading pattern accounts for 11.5% of the total field variability, which is at least three times as large as expected from the null isotropic field. It is characterized by dominant same-sign loadings over India and Southeast Asia, with opposite sign loadings over the Tibetan Plateau, northern Pakistan, and the Pamir and Tien-Shan Mountains. The time series expansion of this mode (DPC1, Fig. 3) correlates well with the hemispherically symmetric SST anomalies characteristic of interdecadal variability in the Pacific Ocean (*7*). This DEOF pattern is associated with persistently weak monsoons in tropical south and Southeast Asia in the mid-14th and early 15th centuries (especially in the period 1351 to 1368) that are similar in timing to that of severe droughts associated with the demise of the Khmer civilization at Angkor in Cambodia (*26*). Other notable large-scale droughts also occurred in the late 16th century (1560 to 1587), at the end of the 17th century (1682 to 1699), during the Strange Parallels period (1756 to 1768), and in an apparent shift toward dry conditions after the mid-1970s (*1*) (fig. S9). Understanding the causes of these earlier droughts may help explain why a late 20th-century trend toward drier conditions and weaker monsoons has occurred over India and Southeast Asia.

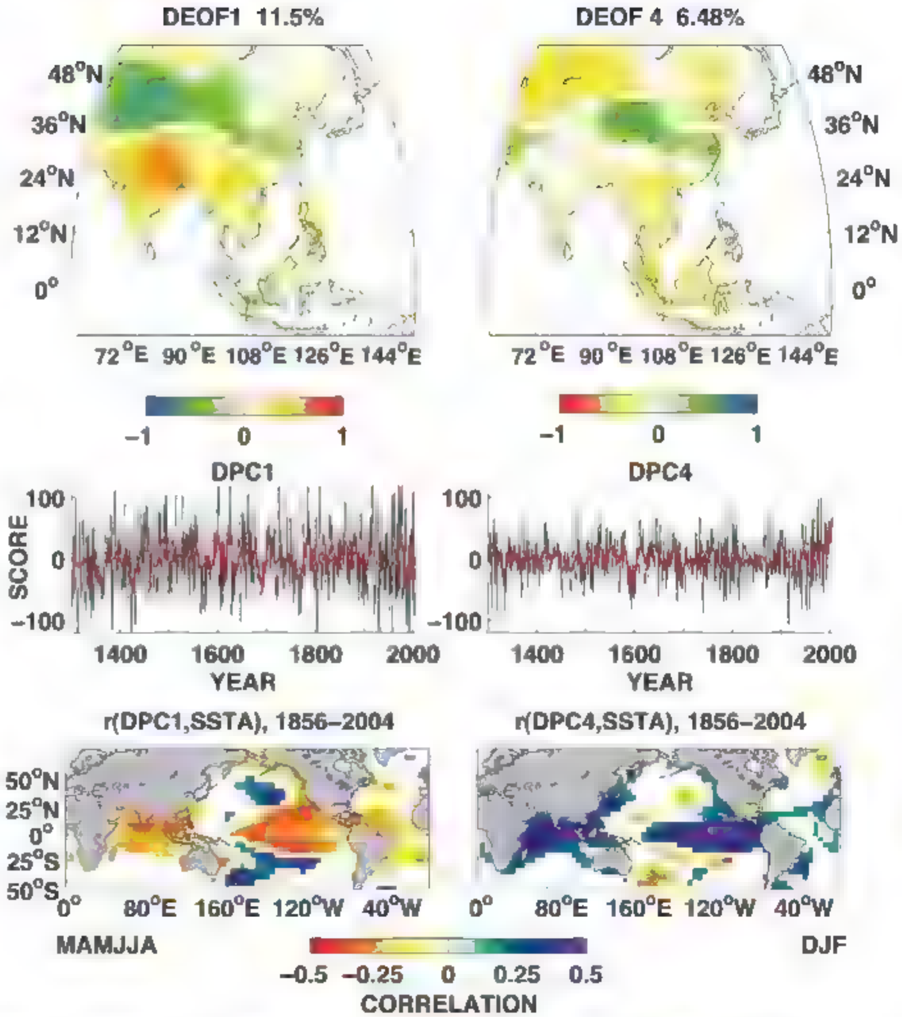

Fig. 3. Spatiotemporal patterns of the MADA since 1300 C.E. Distinct empirical orthogonal function (DEOF) (*25*) analysis of the MADA since the late Medieval period reveals five distinct modes, two of which are shown here and the remainder in (*1*). Middle panels show the time series expansion (DPCs, distinct principal components) of the corresponding spatial modes in the top row. In the bottom row, Pearson correlations with SSTA (*1*) and DEOF/DPC1 are simultaneous with the monsoon and premonsoon season (MAMJJA), whereas the SSTA patterns for DEOF/DPC4 are for the previous winter (DJF) season. Only correlation values significant at 95% confidence are shown.

The remaining significant DEOF modes each account for ~6% of the variance in the reconstructed field since 1300 C.E. For instance, DEOF4 (Fig. 3) is a distinct pattern with strong positive loadings over the eastern Tibetan Plateau. The time series expansion of this mode is positively correlated with eastern equatorial SST anomalies and trends strongly toward more positive PDSI values during the 20th century, suggesting that warm cold tongue SSTs lead to increased moisture availability over the eastern Tibetan Plateau. This finding is consistent with both observations and modeling (*27*, *28*) that show increasing snow accumulation and significant correlations with ENSO variability. Whereas the correlations of the distinct modes with SSTs can only be calculated over the available historical period since 1856 (*1*), the DEOFs are based on the full-field reconstructions since 1300 C.E. and represent large-scale patterns of coherent spatiotemporal covariance that characterize the monsoon region back to the late Medieval period.

The further utility of the MADA for analyzing hemisphere-scale Pacific basin climate dynamics is illustrated in Fig. 4. The late Victorian Great Drought (*18*) (1876 to 1878, Fig. 2D) was characterized by monsoon failure and drought over India and Southeast Asia. Simultaneously, parts of western North America experienced similar anomalously dry conditions, whereas Mexico and the Pacific Northwest were abnormally wet. Although there were persistent mean cold tongue SST warm anomalies during 1876 and 1878 of at least +2°C, this pattern is not the canonical result of a strong eastern Pacific ENSO event (*29*). This may reflect the influence of warm SST anomalies

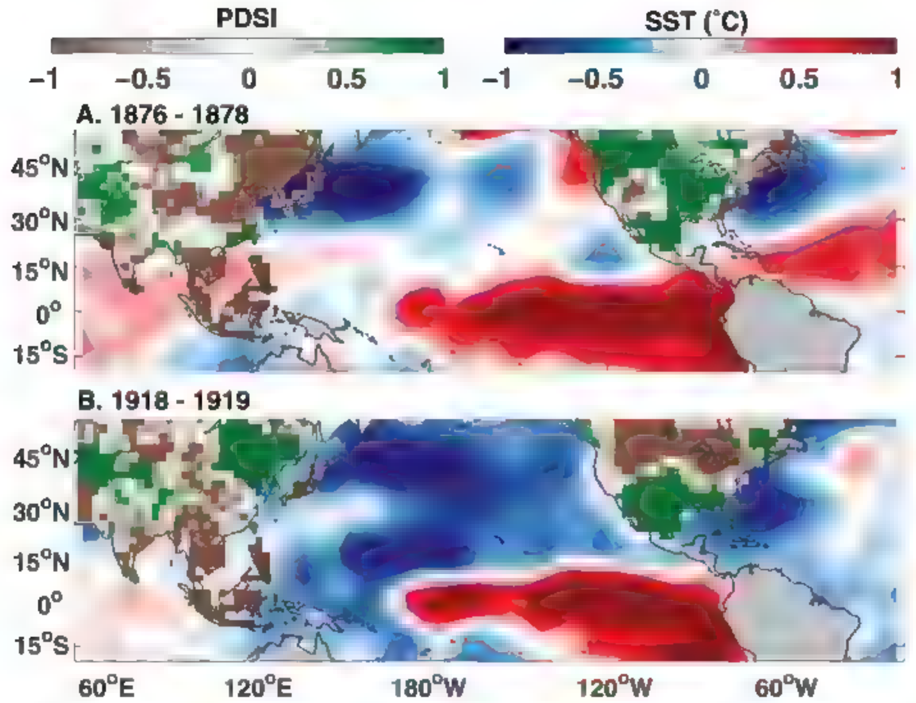

Fig. 4. Pan Pacific drought patterns during (**A**) the Great Drought (1876 to 1878) (*18*) and (**B**) the 1918 to 1919 ENSO event (*30*). During the Great Drought (A), PDSI values are strongly negative (terrestrial, brown-green colormap) over south and Southeast Asia and the Great Basin of North America. Pluvial conditions are reconstructed over the Mexican sector of the North American monsoon region, the Pacific Northwest, and the Tibetan Plateau. The post World War I drought (B) shows pluvial conditions over southern North America and drought to the North, whereas in Asia drought dominates in India and Southeast Asia and southeastern China. Both trans Pacific Basin drought patterns were associated with a strong El Nino event (°C, marine, blue-red colormap) with characteristic positive SST anomalies in the eastern equatorial Pacific (*1*); however, the 19th-century drought has strong positive anomalies over the tropical Atlantic and North Pacific anomalies characteristic of the positive phase of the PDO. The early–20th-century drought shows cold anomalies in both the Atlantic and North Pacific.

in the northeastern Pacific, warm SSTs in the tropical Atlantic, and an extratropical North Pacific typical of the Pacific Decadal Oscillation (PDO).

The 1918 to 1919 El Niño event following the end of World War I is also included as an example in Fig. 4 because of renewed interest in reclassifying its magnitude and global impact (*30*). As compared to the 1876 to 1878 Great Drought, this El Niño event featured canonical wet conditions over the southwestern United States and dry conditions in mainland monsoon Asia and the northern part of North America. This event is associated with a more equatorially constrained SST anomaly pattern, less warming over the Indian Ocean, and cold SSTs in both the Atlantic and North Pacific, which may explain some of the differences between its impact over Asia and North America as compared to the 1876 to 1878 event.

The long-term spatiotemporal modes of Asian monsoon variability are each associated with distinct, but not orthogonal, SST patterns. This result alone suggests that a simple canonical form of ENSO influence is insufficient to explain Asian monsoon variability, and that several spatial "flavors" of forcing exist. For example, the positive trend in moisture evident in DEOF4 in the late 20th century in north central Asia (Fig. 3) suggests an increase in snowfall and soil moisture over the Tibetan Plateau that is consistent with observations (*27*), whereas drier conditions are observed over south and Southeast Asia (DEOF1) particularly since the 1970s. Tropical drought concurrent with apparent increases in winter-spring moisture over the Plateau may therefore be evidence of the different pathways through which Pacific Ocean climate anomalies interact with different components of the monsoon (*28*), and indeed these two modes are inversely related at multidecadal and longer time scales (*1*) ($N = 706$, >30 years, $r = -0.34$, $P = 0.034$; >40 years, $r = -0.40$, $P = 0.015$).

In addition to the long-term context it provides for modern observed variability in Asian climate, the MADA provides critically important targets for climate models to hindcast the spatiotemporal fingerprint and magnitudes of reconstructed monsoon failures over the past millennium in response to forced and internal dynamics. This should allow us to develop a more in-depth, dynamically consistent understanding of Asian monsoon behavior and its global impacts, with improved predictive skill for the future.

References and Notes

1. Materials and methods are available as supporting material on *Science* Online. The Monsoon Asia Drought Atlas is available at http://iridl.ldeo.columbia.edu/SOURCES/.LDEO/.TRL/.MADA/.
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Supporting Online Material

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Materials and Methods
Figs. S1 to S9
Table S1
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Onset of Convective Rainfall During Gradual Late Miocene Rise of the Central Andes

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A decrease in the ratio of ^{18}O to ^{16}O ($\delta^{18}O$) of sedimentary carbonate from the Bolivian Altiplano has been interpreted to indicate rapid surface uplift of the late Miocene Andean plateau (AP). Here we report on paleoclimate simulations of Andean surface uplift with an atmospheric general circulation model (GCM) that tracks oxygen isotopes in vapor. The GCM predicts changes in atmospheric circulation and rainfall that influence AP isotopic source and amount effects. On eastern AP slopes, summer convective precipitation increases by up to 6 millimeters per day (>500%) for plateau elevations that are greater than about 2000 meters. High precipitation rates enhance the isotope amount effect, leading to a decrease in precipitation $\delta^{18}O$ at high elevations and an increase in $\delta^{18}O$ lapse rate. Our results indicate that late Miocene $\delta^{18}O$ depletion reflects initiation and intensification of convective rainfall.

The South American Andes, stretching 7000 km from north to south with average elevations of ~4 km, formed mainly through crustal thickening associated with Cenozoic subduction and convergence between the Nazca Plate and the South American Plate. Despite extensive research on the tectonic and geodynamic evolution of the Andes, the details of the timing, rate, and style of Andean surface uplift remain controversial. Recent elevation reconstructions based on fossil-leaf morphologies (*1*), carbonate clumped-isotope thermometry (*2*), and carbonate oxygen isotopic compositions (*3*) suggest a rapid, recent rise of the central Andes by ~2.5 ± 1 km during the late Miocene. However, this interpretation has been challenged by geological evidence that indicates a more protracted surface uplift history since the late Eocene [~40 million years ago (Ma)] (*4*–*6*).

The most compelling evidence for rapid rise of the Altiplano plateau is a 3- to 4-per mil (‰) decrease in the the ratio of ^{18}O to ^{16}O ($\delta^{18}O$) of ancient soil carbonate nodules between 10.3 and 6.8 Ma (*3*, *7*). In contrast to other paleoaltimetry methods, oxygen isotope paleoaltimetry has been widely applied and is based on isotope fractionation processes that are well understood. Isotope paleoaltimetry typically uses sedimentary carbonate $\delta^{18}O$ as a proxy for ancient meteoric $\delta^{18}O$. In the absence of knowledge about past isotopic lapse rates, carbonate $\delta^{18}O$ is related to surface elevation change using modern isotopic lapse rates. In the modern climate, elevation and meteoric/surface water $\delta^{18}O$ are well correlated [correlation coefficient (r^2) = 0.80] with a global lapse rate of 2.8‰ km^{-1} (*10*). The elevation-$\delta^{18}O$ relationship reflects Raleigh distillation of the heavy isotope (^{18}O) through condensation and precipitation as air masses are adiabatically cooled (*11*).

Precipitation $\delta^{18}O$ and isotopic lapse rates can be influenced by factors other than air temperature, including the water vapor source, mixing between air masses, and isotopic fractionation through mass-dependent processes (*12*). At low latitudes where convective instabilities trigger heavy rainfall, the $\delta^{18}O$ of air masses is correlated to rainfall rates (isotopic amount effect). In these regions, the isotopic lapse rate can deviate substantially from the global average (*13*).

The Andes figure prominently in South American climate and precipitation. Along the eastern Andean plateau (AP), orographic lifting enhances summer convective cells, leading to high rainfall amounts (*14*, *15*). In addition, the Andes block zonal atmospheric flow and intensify low-level flow and vapor transport via the South American low-level jet (SALLJ) (*16*–*18*). The large influence of the Andes on regional climate has led to speculation that surface uplift caused past climate changes that substantially complicate paleoaltimetry interpretations (*13*, *19*).

We used an isotope-tracking atmospheric general circulation model (GCM) (GENESIS) to quantify the influence of Andean surface uplift on rainfall $\delta^{18}O$. Results from three GCM experiments with prescriptions of Andean elevations corresponding to 100% (modern, MOD) and 50% (intermediate, INT) of modern elevations, as well as 250-m elevation (low, LOW), are described (Fig. 1A). All other boundary conditions are identical between the experiments and are prescribed at modern values. Rainfall amounts and intensity are highly seasonal over the central Andes, with >70% of annual AP rainfall occurring in the austral summer. For this

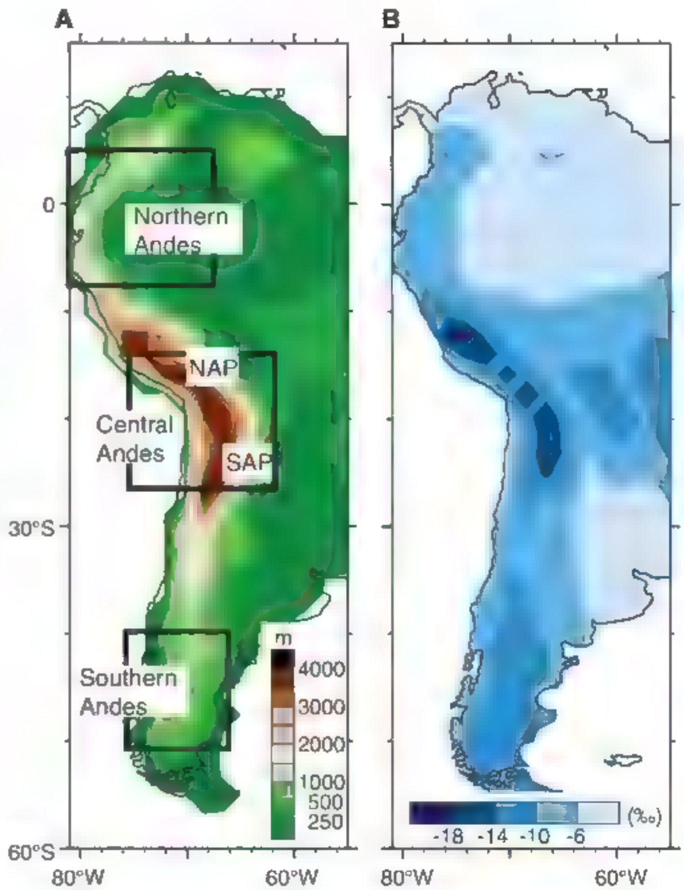

Fig. 1. South American topography (**A**) and mean annual continental rainfall $\delta^{18}O$ (**B**) predicted by the GENESIS AGCM. (A) Modern topography used in the model simulations. Boxes indicate northern, central, and southern Andean domains discussed in the text, Table 1, and Fig. 4. NAP and SAP represent the northern and southern regions of the AP as discussed in the text. (B) Simulated amount-weighted rainfall $\delta^{18}O$. The large negative values (<–14‰) over the Andes compare well with modern observations of meteoric $\delta^{18}O$.

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reason, we focus our analysis below on the December-January-February climatology

GENESIS realistically simulates modern and paleo large-scale climate and circulation patterns as well as spatial variations in precipitation $\delta^{18}O$ (*20, 21*). Our simulated modern precipitation $\delta^{18}O$ is in good agreement with sparse observations from the International Atomic Energy Agency (IAEA) Global Network of Isotopes in Precipitation (*22, 23*). As observed, the simulated mean annual rainfall $\delta^{18}O$ is high (–2 to –6‰) over the Amazon Basin because of isotopic fractionation through evapotranspiration, decreasing to the west over the Amazon Basin. The lowest rainfall $\delta^{18}O$ occurs over the Bolivian Altiplano (<–14‰), which is due to the altitudinal and amount effects, and in southern South America (<–10‰), which is due to a latitudinal temperature effect (Fig. 1B). In agreement with modern observations (*15*), the source of precipitation over the Bolivian Altiplano is primarily water vapor transported via the SALLJ from the Amazon Basin. The main deficiency occurs over southern Brazil, where $\delta^{18}O$ values are too low (by ~4‰) because of not enough vapor transport from the southern Atlantic Ocean during the summer monsoon.

Simulated modern $\delta^{18}O$ lapse rates in the Andes are also in good agreement with observations. In the northern and southern Andes (Fig. 1A), $\delta^{18}O$ lapse rates are 2.58 and 3.36‰ km^{-1}, respectively, and are consistent with observed values of 2 and 3‰ km^{-1} (*24, 25*). In the model, the $\delta^{18}O$ lapse rate over the central AP is 2.12‰ km^{-1}. The $\delta^{18}O$ lapse rate varies along the plateau and is 1.97‰ km^{-1} along an east-west transect from the western Amazon Basin to the northern region of the plateau (14° to 18° S, 65° to 70°W). The predicted lapse rate for this transect is consistent with observed lapse rates that range from 2.31 ± 0.32‰ km^{-1} to 1.46 ± 0.67‰ km^{-1} for wet (1984) and dry (1983) years (*26*).

Andean surface uplift from 250 m to modern elevations substantially reduces precipitation $\delta^{18}O$ over the Andes Mountains and the AP. Over the northern and southern Andes, $\delta^{18}O$ decreases by 1 to 4‰. Over the central Andes, the decrease is greater, up to ~10‰ (Fig. 2A), and correlates with changes in precipitation amount. However, the decrease in precipitation $\delta^{18}O$ is not systematic with surface elevation increase. With an increase in the Andes from low to one-half modern elevations, rainfall $\delta^{18}O$ decreases by ~8‰ in the northern AP (~10° to 17°S) but increases by up to ~4‰ on the southern AP (~20° to 25°S) (Fig. 2B). With further uplift to modern heights, rainfall $\delta^{18}O$ decreases by 1 to 3‰ over most of the Andes. In the southern AP, the rainfall $\delta^{18}O$ decreases by 5 to 10‰ and corresponds with a significant increase in precipitation (Fig. 2C).

Our results indicate that changes in rainfall and rainfall $\delta^{18}O$ are different for early (INT-LOW) and late (MOD-INT) stage uplift. Thus, variations in $\delta^{18}O$ preserved in sedimentary carbonates can only be partially explained by cooling associated with surface uplift. For example, if adiabatic cooling and associated changes in saturation vapor pressure were the predominant influence on precipitation $\delta^{18}O$, then the $\delta^{18}O$ decrease should be nearly systematic with an increase in surface elevation (fig. S1). Instead, changes in $\delta^{18}O$ with surface uplift are linked to three major summertime circulation changes: (i) formation and strengthening of the SALLJ; (ii) southward shift and intensification of the Chaco Low, the subtropical high, and the midlatitude westerlies, and (iii) blocking of low-level flow to and from the Pacific Ocean (Fig. 3).

Surface uplift causes the SALLJ to intensify and shift westward toward the Andes (Fig. 3, B and C, gray arrows). Intensification of the jet enhances low-level vapor transport from the Amazon Basin along the eastern flanks of the central Andes and into central South America. To the northeast of the Andes, the enhanced transport of isotopically enriched vapor from the Amazon leads to an increase in precipitation $\delta^{18}O$ (Fig. 2B). The formation of the SALLJ with initial uplift leads to large (>400%) increases in precipitation along the central Andes (Fig. 2B), predominantly (>90%) due to convective activity

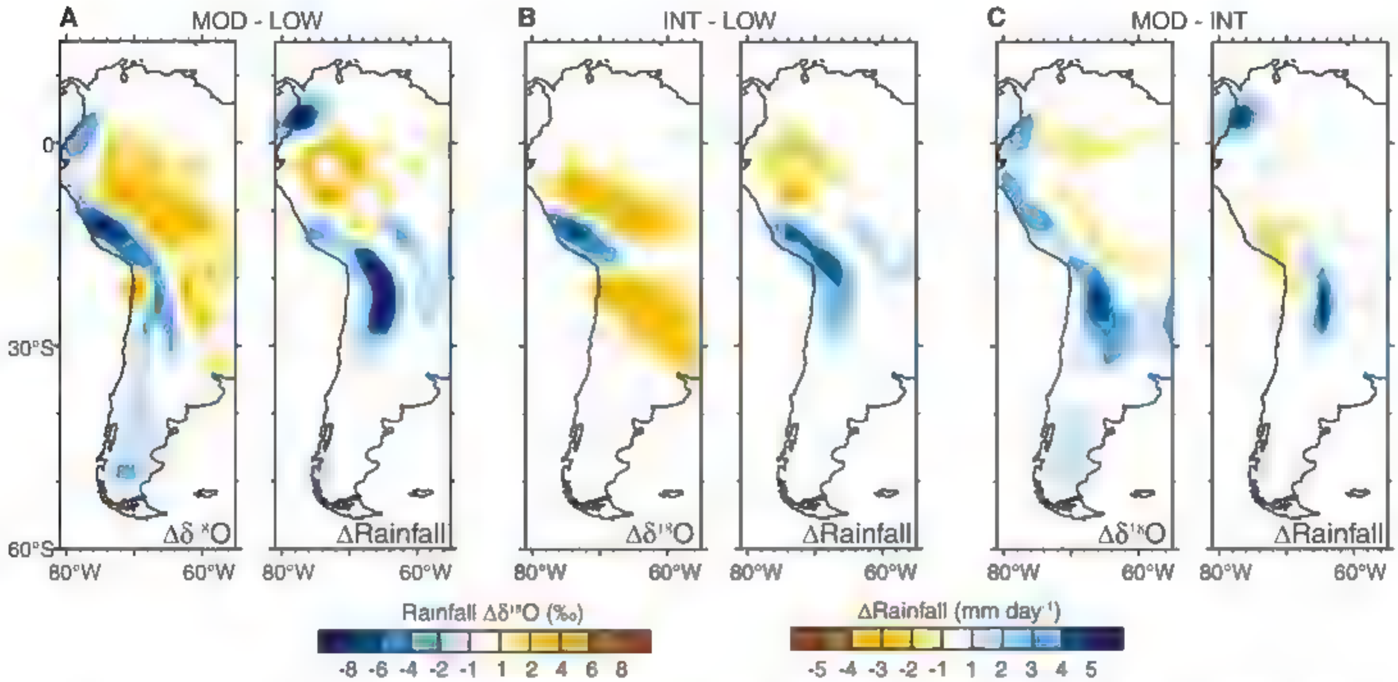

Fig. 2. Predicted change (Δ) in summer (December, January, and February) amount-weighted rainfall $\delta^{18}O$ and rainfall rate due to Andean surface uplift. (**A**) Total simulated change in rainfall $\delta^{18}O$ and rainfall rate due to Andean surface uplift. In (**B**), differences in rainfall $\delta^{18}O$ and rate between the INT and LOW experiments are plotted, showing the influence of uplift to 50% of Andean elevations. In (**C**), differences in rainfall $\delta^{18}O$ and rate between the MOD and INT experiments are shown. Convective precipitation accounts for nearly the entire precipitation signal. The surface-uplift amounts represented by (B) and (C) are similar, yet the simulated isotopic responses are not. The differences in response are due to changes in atmospheric circulation and rainfall physics and indicate that factors other than surface elevation affect rainfall $\delta^{18}O$. Also, there is a correspondence between increases in precipitation rate on and near the Altiplano and decreases in rainfall $\delta^{18}O$. Predicted mean annual $\Delta\delta^{18}O$ is qualitatively similar to summer $\Delta\delta^{18}O$ (fig. S3).

triggered by latent heat release as air masses converge on the plateau. Increased convective precipitation leads to a substantial (>8‰) decrease in rainfall $\delta^{18}O$ in the northern central Andes (~10° to 17°S) because of the amount effect (27).

Early uplift of the Andes also leads to southeastward displacement of the subtropical high away from the growing plateau and an associated southward shift in the midlatitude westerlies. The shift and strengthening of the subtropical high alters the balance of vapor sources in the southern central Andes (between ~20° and 25°S) from primarily mid-latitude low $\delta^{18}O$ regions in the LOW experiment to enhanced flow from the more $\delta^{18}O$–enriched subtropical regions in the INT simulations (Fig. 3, B and C). These changes in the low-level circulation with initial uplift result in an increase in vapor and rainfall $\delta^{18}O$ in the southern central Andes, despite elevation gain (Fig. 2B).

The rise of the Andes to modern elevations of ~4 km leads to blocking of low-level westerly flow from the South Pacific to the southern AP (Fig. 3A). At low elevations (INT and LOW), anticyclonic flow transports relatively dry cool air from the Pacific Ocean to the southern AP (Fig. 3, B and C). With increasing elevation (MOD), the convergence of warm, moist air from the Chaco region triggers convection and high convective rainfall along the eastern slopes of the central Andes (~20° to 25°S), causing $\delta^{18}O$ to decrease by >8‰ (27) (Fig. 2C). Over the northern and southern Andes, surface uplift to modern elevations causes a decrease in rainfall $\delta^{18}O$ of 1 to 4‰ (Fig. 2C), which is consistent with isotopic depletion through adiabatic cooling.

The changes in circulation and precipitation predicted by the GENESIS GCM, including the formation and strengthening of the SALLJ, shifting of the Chaco Low and westerlies, and intensification of convective precipitation, agree with higher-resolution climate simulations of South America (17, 18). Higher-resolution (60-km grid spacing) regional experiments also indicate that deep convection occurs at plateau heights that are >50% of modern, or ~2000 m (17). We verified this result with additional high-resolution (25-km grid spacing) regional simulations over central South America using the method of (17). These experiments confirm that precipitation on the eastern slopes of the central Andes increases abruptly when Andean elevations reach ~70% of modern elevations (Fig. 4A).

Changes in isotopic source and amount effects with surface uplift also affect isotopic lapse rates. Over the AP, where the elevation increase in our experiments is greatest, the $\delta^{18}O$ lapse rate is 1.1‰ km^{-1} in the INT experiment, which is one-half of the MOD lapse rate (Table 1). This result has implications for the AP uplift history, because oxygen isotope paleoaltimetry assumes that the modern $\delta^{18}O$ lapse rate is representative of times when the mountains were lower.

To demonstrate the potential impact of convective rainfall intensification on paleoaltimetry estimates, we show a linear regression model of simulated central Andean rainfall $\delta^{18}O$ and elevation for the INT and MOD experiments (Fig. 4B). At an elevation of 2000 m, rainfall $\delta^{18}O$ differs by −1.7‰ between these experiments, a difference that is related only to climate change and mainly to isotopic depletion through rainout. If a $\delta^{18}O$ signal of −1.7‰ were found in the stratigraphic record, it would be interpreted with standard paleoaltimetry techniques based on modern $\delta^{18}O$-elevation relationships as an elevation gain of ~700 m, when in fact no surface uplift had occurred. Extrapolation of the linear regression model for the INT experiment to higher elevations leads to larger rainfall $\delta^{18}O$ differences between the MOD and INT experiments, a trend that is consistent with progressive rainout in the MOD case as air masses ascend the AP slopes. At an elevation of 3800 m, which is the modern elevation of the late Miocene carbonate deposits used to estimate central Andean paleoaltimetry (3), rainfall $\delta^{18}O$ differs by −4.1‰, equaling the isotopic signal preserved in late Miocene deposits. Our point is not to argue against AP surface uplift—in fact, the onset of convection rainfall requires it—but to demonstrate that a

Table 1. Mean annual precipitation $\delta^{18}O$ lapse rates for northern, central, and southern Andean regions as shown in Fig. 1. Lapse rates are estimated by calculating a linear regression between amount weighted annual precipitation $\delta^{18}O$ and elevation. No estimates are made for the LOW experiment, which has no significant Andean topography by design. Correlation coefficients are shown in parentheses.

Region	MOD (‰ km^{-1})	INT (‰ km^{-1})
Northern Andes	3.07 (−0.74)	2.71 (−0.54)
Central Andes	2.12 (−0.78)	1.10 (−0.24)
Southern Andes	4.55 (−0.59)	4.57 (−0.40)

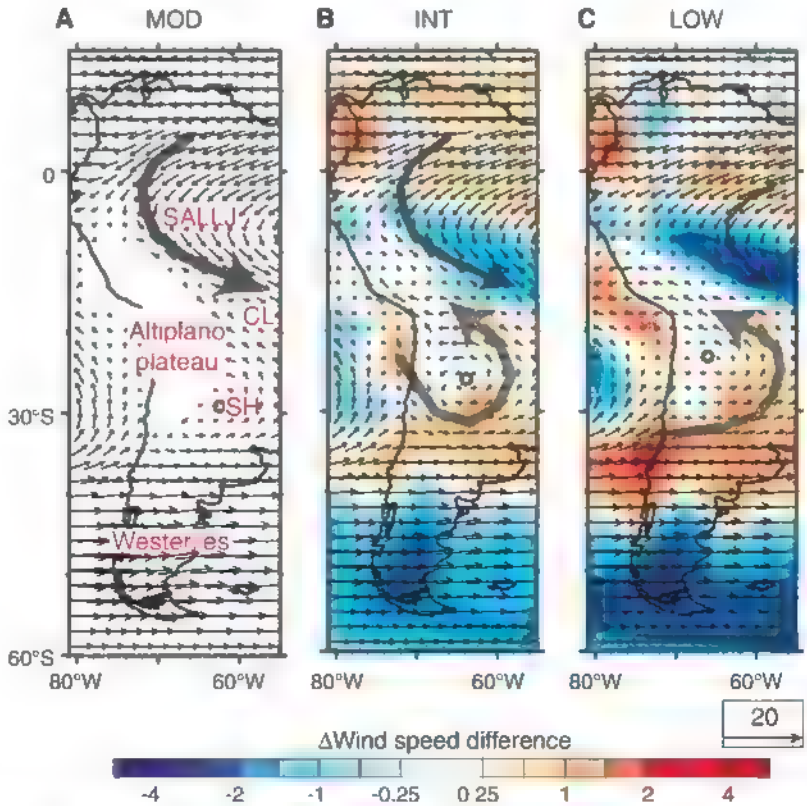

Fig. 3. Simulated summer low-level (800-mbar) circulation for the three uplift scenarios: **(A)** MOD (modern elevation), **(B)** INT (intermediate elevation), and **(C)** LOW (low elevation). Vectors are missing in (A) where the flow intersects high topography. The difference in 800-mb wind speed (in meters per second) from the control (MOD) case (INT–MOD, LOW–MOD) is shaded; positive (red) values represent faster flow; negative (blue) values represent slower flow. Surface uplift modifies the low-level circulation. Most notably, the SALLJ intensifies; the Chaco Low (CL), subtropical high (SH), and midlatitude westerlies migrate southward and become stronger. Yellow-filled circle indicates the center of the subtropical high; arrows indicate low-level circulation discussed in text.

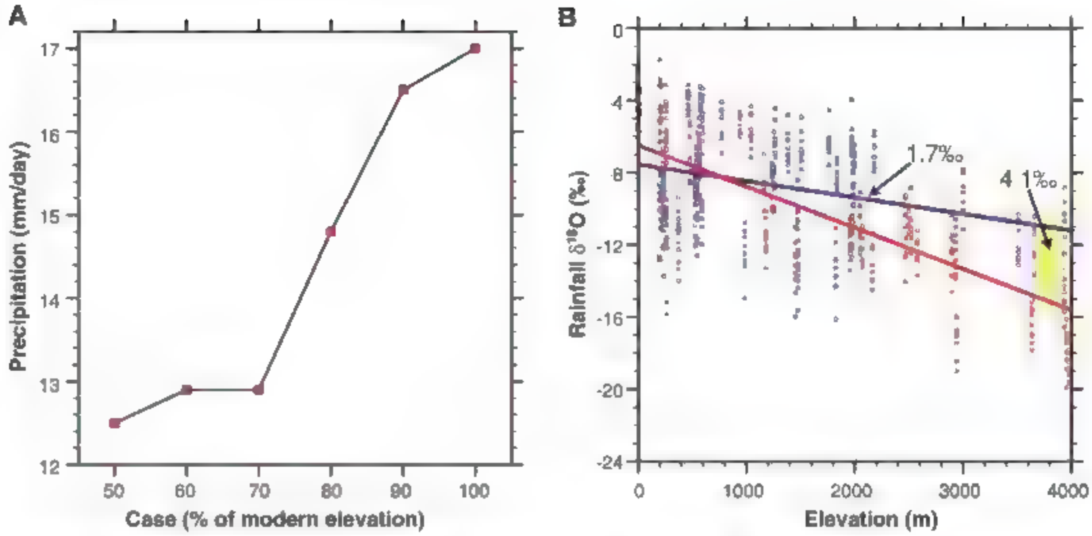

Fig. 4. (**A**) Summer precipitation on the eastern AP as a function of elevation. The simulated precipitation rates are from five high-resolution (25-km horizontal grid spacing) RegCM experiments with Andean heights varying as a percentage of modern height as in (*17*). (**B**) GENESIS precipitation $\delta^{18}O$ versus elevation in the central Andes. Symbols represent annual average amount-weighted precipitation $\delta^{18}O$ from individual grid points within a central Andes domain (Fig. 1, center). Values are from the MOD (blue) and INT (red) experiments. In agreement with observations, the model simulates a decrease in precipitation $\delta^{18}O$ with elevation and interannual variability in precipitation $\delta^{18}O$. The blue line shows the linear regression for the MOD and the red line shows it for the INT experiment. The linear regression line for the INT experiment is linearly extrapolated from 2000 to 4000 m. There is an offset in both the intercept and slope of the regression line between experiments due to differences in the isotopic amount effect. Yellow bars highlight oxygen isotopic offsets of ~1.7 and 4.1‰ between these experiments at 2000 and 3800 m, respectively.

substantial portion of the isotopic signal reflects climate change. In the northern and southern Andes, surface uplift has a minor influence on simulated rainfall rates and on isotopic lapse rates (Table 1).

Our GCM results resolve an inconsistency in the paleoaltimetry interpretation of carbonate $\delta^{18}O$ data. Previous estimates using modern lapse rates suggest that paleoelevations were below sea level (700 ± 1000 m) before rapid uplift at 10 3 Ma (*2*, *3*), which is at odds with geological evidence Our results indicate that before the initiation of convective rainfall, the isotopic lapse rate would have been smaller; consequently, relatively large absolute $\delta^{18}O$ values would have corresponded to higher elevations than today. In fact, simulated annual rainfall $\delta^{18}O$ (8.5‰) for an AP region at ~2000 m elevation in the INT experiment is consistent with $\delta^{18}O$ of water (6.9 to −10.5‰) derived from Miocene carbonates that were previously interpreted to have been deposited near sea level (fig. S2). Taken together, our results indicate that the late Miocene rapid decrease in $\delta^{18}O$ results from changes in low-level winds and the onset of convective precipitation. The simulated onset of convective rainfall is supported by sedimentologic, paleontologic, and stable-isotope evidence for a shift from arid to humid conditions in the central Andes (*28*–*31*).

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Figs. S1 to S3
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Complexity and Diversity

Michael Doebeli* and Iaroslav Ispolatov*

The mechanisms for the origin and maintenance of biological diversity are not fully understood. It is known that frequency-dependent selection, generating advantages for rare types, can maintain genetic variation and lead to speciation, but in models with simple phenotypes (that is, low-dimensional phenotype spaces), frequency dependence needs to be strong to generate diversity. However, we show that if the ecological properties of an organism are determined by multiple traits with complex interactions, the conditions needed for frequency-dependent selection to generate diversity are relaxed to the point where they are easily satisfied in high-dimensional phenotype spaces. Mathematically, this phenomenon is reflected in properties of eigenvalues of quadratic forms. Because all living organisms have at least hundreds of phenotypes, this casts the potential importance of frequency dependence for the origin and maintenance of diversity in a new light.

There are two major aspects underlying the general question of how phenotypic diversity originates and is maintained within a population or species. First, standing genetic variation within a single species is typically much greater than would be expected if evolution were solely due to an adaptive optimization process (*1*–*3*). Second, the mechanisms that diversify lineages into multiple diverging descendent lineages remain elusive (*4*, *5*). Much pertinent evolutionary theory has been developed (*5*–*11*), including neutral evolution, mutation-selection balance, and frequency-dependent selection (also referred to as balancing selection). With negative frequency dependence, rare types have an advantage, which can contribute to the maintenance of genetic variation (*3*) and the origin of new species (*12*, *13*). Nevertheless, whether frequency-dependent selection is of general importance for biological diversity remains unclear. The vast majority of models have considered evolution in simple one-dimensional (1D) phenotype spaces, in which frequency dependence needs to be strong to generate diversity.

We extended classical models for frequency-dependent competition from one to many phenotypic dimensions. In the basic 1D model, which has a long tradition in ecological and evolutionary theory (*12*, *14*–*18*), individuals have a scalar (that is, 1D) phenotype x that determines resource preferences. If individuals have similar preferences, they will consume similar types of food and hence experience strong competition. The competitive impact between two individuals with phenotypes x and y is described by the competition kernel $\alpha(x,y)$, which is assumed to be a unimodal function of the phenotypic distance $|x-y|$ that has its maximum at $|x-y|=0$. This generates a frequency-dependent component of selection: Individuals with a rare phenotype have only a few similar individuals in the population, and hence experience large competitive impacts from only a few individuals, whereas those with common phenotypes experience large competitive impacts from many other individuals.

If $\varphi(x)$ is the density distribution of phenotypes, its dynamics is given by the logistic partial differential equation

$$\frac{\partial\varphi(x)}{\partial t} = r\varphi(x)\left(1-\frac{\int\alpha(x,y)\varphi(y)dy}{K(x)}\right) \quad (1)$$

Here $\int\alpha(x,y)\varphi(y)dy$ is the effective density experienced by x individuals, which is a weighted sum over the whole population $\varphi(y)$, with the weights equal to the competitive impact of y individuals on x individuals. The function $K(x)$ is the carrying capacity function, giving the equilibrium density of a hypothetical population that only contains x individuals. $K(x)$ is assumed to be unimodal with a maximum at $x=0$ and represents a stabilizing component of selection for trait value $x=0$. (The intrinsic growth rate r is assumed to be independent of the phenotype x and is set to 1.) We assume the following functional forms for the competition kernel and the carrying capacity

$$\alpha(x,y) = \exp(-a|x-y|^{n_\alpha}) \quad (2)$$

$$K(x) = K_0\exp(-k\,x^{n_K}) \quad (3)$$

These functions are symmetric because of the assumptions that they depend on the absolute value |...| of their argument. The parameters $a>0$ and $k>0$ measure the relative importance of the frequency-dependent component and the stabilizing component of selection, and n_α and n_K are shape parameters, which we assume to be real numbers ≥2 to ensure that the functions are at least twice differentiable at 0. K_0 scales the overall population size. The dynamics of the model in Eq. 1 is well known in the so-called Gaussian case, in which the shape parameters are $n_\alpha = n_K = 2$. If $k>a$, the stabilizing component of selection dominates and hence the dynamics of Eq. 1 converges to a delta peak centered at $x=0$. In particular, all variation is lost from the population in this case. Conversely, if $k<a$, competition is more localized in phenotype space as compared to the width of the carrying capacity curve, so that the frequency-dependent component of selection dominates. In such cases, the dynamics of Eq. 1 converge to an equilibrium distribution that is proportional to a normal distribution with a positive variance, and hence variation is maintained. In essence, this is the basis for the claim that strong frequency dependence can maintain diversity (Fig. 1).

It is important to note that for competition kernels and carrying capacities that are non-Gaussian, the maintenance of diversity due to

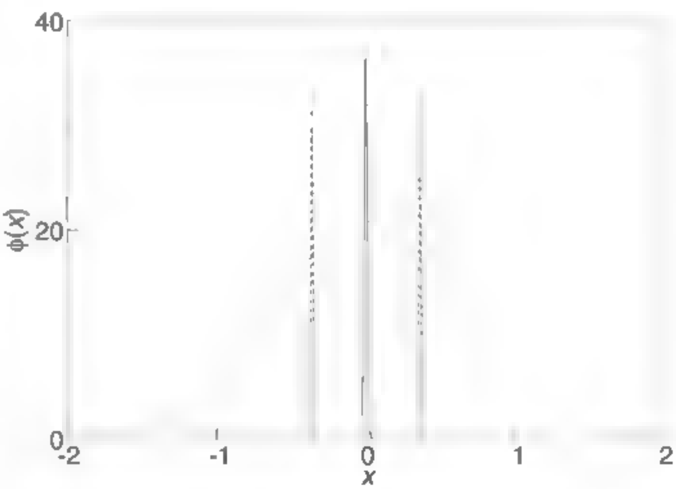

Fig. 1. Equilibrium population density for the Gaussian model (Eq. 1), with $n_\alpha = n_K = 2$ in Eqs. 2 and 3, and $a = k = 1$ (solid line) and $a = 2$, $k = 1$ (dotted line). In the long time limit, the former case converges to a delta peak centered at $x = 0$ and hence corresponds to loss of genetic variation, whereas the latter distribution retains a positive variance. The two narrow peaks given by the dashed lines represent maintenance of variation in the form of a bimodal equilibrium distribution for platykurtic competition and carrying capacity functions, $n_\alpha = n_K = 4$ in Eqs. 2 and 3, with $a = 2$ and $k = 1$. In the long time limit, this distribution converges to two delta peaks. It is straightforward to introduce mutations into the model given by Eq. 1; for example, by adding a diffusion term. This would result in qualitatively very similar results, except that the delta peaks would be replaced by narrow peaks with a small but positive variance due to mutation.

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strong frequency dependence in Eq. 1 may not result in a unimodal equilibrium distribution (19–22). For example, with $n_a = n_k = 4$, and hence with platykurtic functions that fall off less sharply from the maximum than Gaussian functions, the case where the frequency-dependent component is stronger than the stabilizing component of selection leads to multimodal equilibrium distributions (Fig. 1), in which the different modes represent different phenotypic clusters. But regardless of the exact form in which variation is maintained, the basic model (Eq. 1) illustrates that in 1D phenotype spaces, strong frequency dependence is needed to maintain diversity.

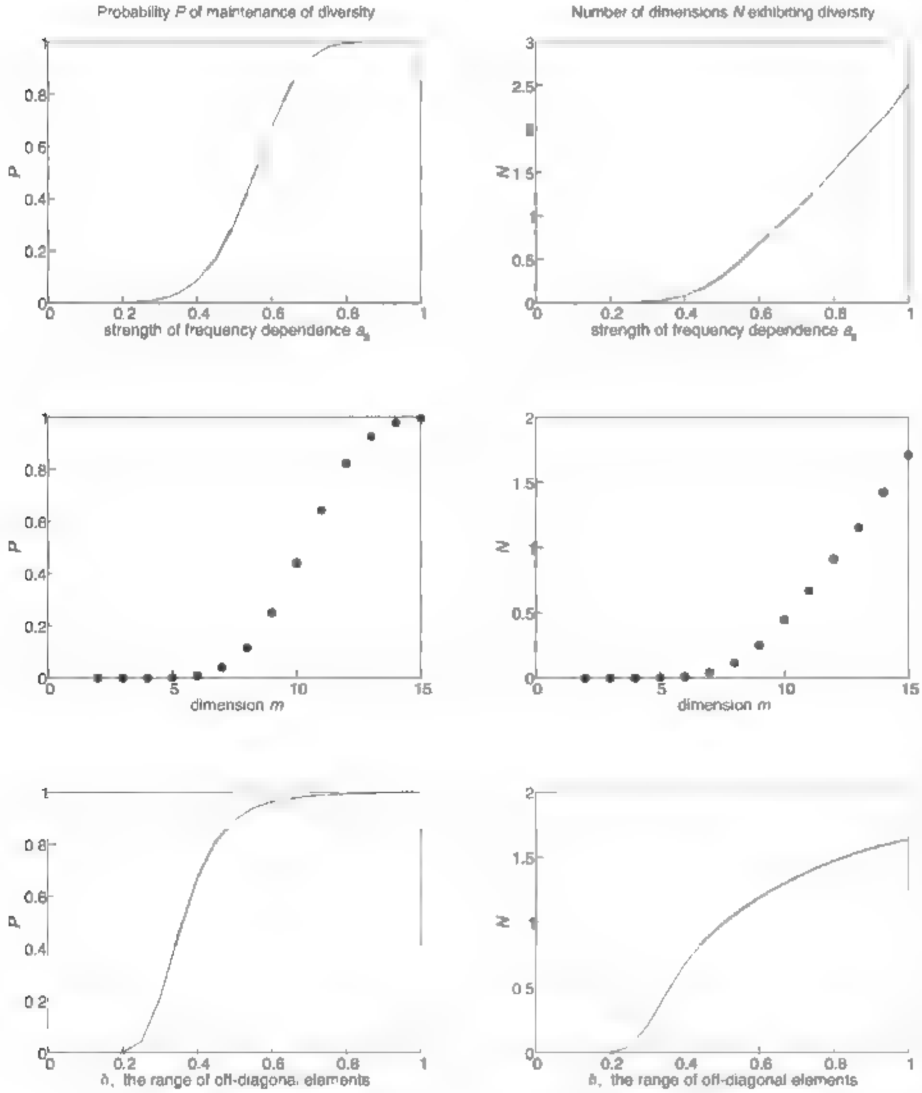

Fig. 2. Effects of interactions between phenotypic components on diversity. The starting points are diagonal matrices K with identical diagonal elements $k_{ii} = 1$, and A with identical diagonal elements $a_{ii} < 1$, in the Gaussian model (Eq. 6), so that the condition $a > k$ for the maintenance of diversity is not satisfied in any phenotypic direction. The panels shows results due to the addition of uniformly randomly chosen off-diagonal elements in the range $[-\delta,\delta]$ at each off-diagonal position in both matrices. Only realizations when both A and K are positive definite are considered. The first column shows the probability that this results in the condition for diversification $a > k$ satisfied in at least one direction after simultaneous diagonalization of the resulting quadratic forms (23). This probability is shown as a function of the diagonal elements a_{ii} in the starting matrix A (first row), as a function of the dimension of phenotype space m (second row), and as a function of the parameter δ determining the range from which the off-diagonal elements are drawn (third row). The right-hand column shows the average number of phenotypic dimensions in which diversification occurs after the addition of random off-diagonal elements. Results were obtained from 10^5 random samplings of k_{ij} and a_{ij}, with standard diagonalization techniques applied to the resulting quadratic forms. The parameters that are fixed are the dimension of phenotype space $m = 5$ and the range $\delta = 0.2$ for the first row, $a_{ii} = 0.2$ and $\delta = 0.2$ for the second row, and $m = 5$ and $a_{ii} = 0.2$ for the third row. The probability of diversification becomes large even if $k_{ii} - a_{ii}$ is substantially larger than δ (top left panel). Also, even for k_{ii} much larger than a_{ii} (that is, even when stabilizing selection is overwhelming frequency dependence in each component direction), the probability of diversification due to off-diagonal elements approaches 1 for high dimensions m (middle left panel).

We extend the Gaussian model (Eq. 1) with $n_a = n_k = 2$ to multiple phenotypic dimensions $x_1,\ldots,x_m$ by assuming that in each direction x_i there is a frequency-dependent component and a stabilizing component of selection, described by parameters a_{ii} and k_{ii}, respectively. The competition kernel is

$$\alpha(x_1,\ldots,x_m,y_1,\ldots,y_m) = \exp(-(x-y)\cdot A\cdot(x-y)^T) \quad (4)$$

where A is an $m \times m$ matrix and where $x = (x_1,\ldots,x_m)$, $y = (y_1,\ldots,y_m)$ [so that $(x-y) = (x_1-y_1,\ldots,x_m-y_m)$], and y^T is the transposed vector. Here the various scalars x_i should be thought of as observable phenotypic traits, such as body size or some other morphological feature, behavior, coloration, or a metabolic property. Such traits are not only biologically identifiable but are also often controlled by distinct sets of genes and/or signaling pathways. If there are no interactions between the different components x_i of the m-dimensional phenotype (where interaction is understood in the statistical sense), A is a diagonal matrix with entries $a_{11},\ldots,a_{mm}$. In this case, $x\cdot A\cdot y^T = a_{11}(x_1-y_1)^2+\ldots+a_{mm}(x_m-y_m)^2$, and the competitive impact between individuals with phenotype vectors $x = (x_1,\ldots,x_m)$ and $y = (y_1,\ldots,y_m)$ is simply a product of the impacts of the phenotypic components. However, in reality, different phenotypic components are rarely ecologically independent and will typically interact to affect competition in a complicated nonmultiplicative way. For example, the competitive impact of an individual with beak length y_1 and wing span y_2 on an individual with beak length x_1 and wing span x_2 may be larger than the product of the competitive impacts measured in each phenotypic direction separately, if birds with both a large beak and large wings tend to be more aggressive. This would be reflected by an off-diagonal element $a_{12} < 0$ in the matrix A. Similarly, the competitive impact of bacteria secreting amounts y_1 and y_2 of two toxins may be less than the product of the competitive impacts induced by y_1 and y_2 separately, if the effectiveness of one toxin is reduced in the presence of another toxin, which would be reflected by an off-diagonal element $a_{12} > 0$. Without loss of generality, we assume A, representing the quadratic form (Eq. 4), to be a symmetric matrix.

For the stabilizing component of selection, we may assume that in each phenotypic direction, the location of the maximum of the carrying capacity is at $x_i = 0$. The carrying capacity is then given by a function

$$K(x_1,\ldots,x_m) = K_0 \exp(-x\cdot K\cdot x^T) \quad (5)$$

where K is an $m \times m$ matrix and where $x = (x_1,\ldots,x_m)$. Again, if there are no interactions

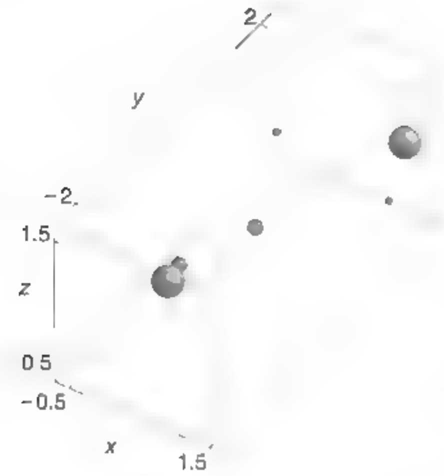

Fig. 3. Equilibrium distribution of the 3D non-Gaussian model (Eqs. 9 and 10) with matrices

$$A = \begin{pmatrix} 0.32 & 0.55 & 0.28 \\ 0.55 & 0.32 & -0.21 \\ 0.28 & -0.21 & 0.32 \end{pmatrix} \text{ and}$$

$$K = \begin{pmatrix} 1 & -0.018 & 0.686 \\ -0.018 & 1 & 0.552 \\ 0.686 & 0.552 & 1 \end{pmatrix}$$

In all three phenotypic dimensions, stabilizing selection dominates frequency-dependent selection (taken in each direction separately, the above parameters correspond to $a = 0.32$ and $k = 1$ in Eqs. 2 and 3, with $n_\alpha = n_K = 4$), but phenotypic interactions in the form of nonzero off-diagonal elements generate diversification into a sum of delta peaks whose location in the 3D phenotype space is indicated by the spheres. The size of the spheres represents the weight of the corresponding delta peak. Projections onto axes x, y, and z show diversification in all three phenotypic dimensions [fig. S1 in (23)].

between the different phenotypic components, K is a diagonal matrix with entries $k_{11}, \ldots, k_{mm}$, and $x \cdot K \cdot x^T = k_{11}x_1^2 + \ldots + k_{mm}x_m^2$, so that the carrying capacity of phenotype $x = (x_1,\ldots,x_m)$ is simply a product of the carrying capacities of the phenotypic components. In general, phenotypes affect the carrying capacity in a more complicated way, which is again reflected in nonzero off-diagonal elements in the matrix K. For example, a predator feeding on two different species with efficiencies determined by two traits x_1 and x_2 could have a nonzero off-diagonal matrix element k_{12} in its carrying capacity due to the fact that more effective predation on one species affects the availability of the other species through the dynamics of the entire food web. Without loss of generality, we choose K to be a symmetric matrix. Also, we assume that the carrying capacity has a unique maximum at $x = 0$ and that the competition kernel has a line of maxima at $y = x$. This implies that both matrices A and K are positive definite (that is, all their eigenvalues are real and > 0).

The extension of the Gaussian model (Eq. 1) to multiple dimensions is thus determined by the two quadratic forms A and K, and the dynamics of the multidimensional phenotype density distribution $\varphi(x_1,\ldots,x_m)$ are given by

$$\frac{\partial\varphi(x_1,\ldots,x_m)}{\partial t} = \varphi\left(1 - \frac{\int\alpha(x_1 - y_1,\ldots,x_m - y_m)\varphi(y_1,\ldots,y_m)\,dy_1\ldots dy_m}{K(x_1,\ldots,x_m)}\right) \quad (6)$$

where α and K are given by Eqs. 4 and 5.

If there are no interactions between different phenotypic dimensions, and hence the matrices A and K are diagonal, the conditions for the maintenance of diversity in the multidimensional model are essentially the same as in the 1D model (Eq. 1): Diversity is maintained if and only if $a_{ii} > k_{ii}$ for at least one phenotypic component i. This shows that the dimensionality alone has no effect on the maintenance of diversity. This changes, however, if there are interactions between phenotypic components, so that A and K are not diagonal, as is most easily illustrated in the case of two phenotypic components. Assuming that $a_{11} = k_{11} = a_{22} = k_{22} = 1$, so that in each dimension, the system is exactly on the boundary of the parameter region in which diversity is maintained, with interactions between the two phenotypes, the matrices A and K have the form

$$A = \begin{pmatrix} 1 & a_{12} \\ a_{12} & 1 \end{pmatrix} \quad K = \begin{pmatrix} 1 & k_{12} \\ k_{12} & 1 \end{pmatrix} \quad (7)$$

where a_{12} and k_{12} may be positive or negative. The matrices A and K can be diagonalized simultaneously by the linear change of coordinates $y_1 = (x_1 - x_2)/\sqrt{2}$ and $y_2 = (x_1 + x_2)/\sqrt{2}$. In these new, diagonal coordinates, the quadratic forms A and K become

$$A = \begin{pmatrix} 1 - a_{12} & 0 \\ 0 & 1 + a_{12} \end{pmatrix} K = \begin{pmatrix} 1 - k_{12} & 0 \\ 0 & 1 + k_{12} \end{pmatrix} \quad (8)$$

Hence the dynamical system (Eq. 6) is equivalent to a system where the phenotypic components do not interact, but where the parameters a_{ii} and k_{ii} have the values $1 \pm a_{12}$ and $1 \pm k_{12}$ instead of 1. In general, the interaction effects between phenotypes are different for competition and for the carrying capacity (that is, $a_{12} \neq k_{12}$), and it immediately follows that in the new coordinate system, the condition for diversification is satisfied in one of the two dimensions (we either have $1 - a_{12} > 1 - k_{12}$, or $1 - a_{12} > 1 + k_{12}$). The direction satisfying the diversification condition is a linear combination of the original phenotypic axes (more precisely, the direction of diversification is either the diagonal or the antidiagonal in the original phenotype space). Nevertheless, if diversification occurs along this composite axis, it also occurs in the two original axes. This shows that no matter what phenotypic interactions are assumed, they always generate robust diversification in 2D systems that are only on the brink of diversification without interactions.

It turns out that this is a very general and powerful mechanism for the maintenance of diversity. In dimensions higher than 2, the arguments are a bit more complicated, but it is also true that starting out with coordinates $x_1,\ldots,x_m$ such that $a_{ii} = k_{ii}$ for all i (that is, such that in each isolated phenotypic direction, the system is on the brink of diversification), the addition of interactions between phenotypes generates robust diversification. More precisely, with the addition of off-diagonal elements in A and K, there is a change of coordinates such that the corresponding quadratic forms $\hat{A}$ and $\hat{K}$ are diagonal and such that $\hat{a}_{ii} > \hat{k}_{ii}$ for at least one i, so that diversity is generated in at least one direction (and often many) of the new phenotypic coordinate system. The analytical arguments for the diversifying effects of interactions between phenotypic components provided in (23) are valid for the case $a_{ii} = k_{ii}$, but similar diversifying effects also occur in more general situations. These effects are independent of the sign of the off-diagonal elements in the matrices A and K and independent of whether only A, only K, or both A and K have off-diagonal elements.

More generally, if one starts out with phenotypic dimensions $x_1,\ldots,x_m$ for which $a_{ii} = k_{ii} - \varepsilon$ with $\varepsilon > 0$, so that variation is not maintained in any of the phenotypic components, the addition of off-diagonal elements in A and K can still lead to the maintenance of diversity (Fig. 2). For example, if $m = 2$, and if we assume randomly distributed off-diagonal elements in A and K in the range $(-\delta,\delta)$, then the probability that the system given by Eq. 6 exhibits diversity at equilibrium is $(1 - \varepsilon/2\delta)^2$ (23). Thus, even if the stabilizing component of selection dominates the frequency-dependent component of selection in each of the phenotype directions x_i, interactions between the x_i directions often generate diversity. Moreover, the higher the dimension m of phenotype space, the stronger is this effect, so that for very large m, interactions between the phenotypes can be weak and yet still generate diversity even if frequency dependence is very weak, and hence net selection is strongly stabilizing, in each of the phenotypic components (Fig. 2). Increasing the dimension of phenotype space not only makes the maintenance of diversity more likely, but also increases the amount of diversity maintained; that is, the variance of the equilibrium distributions.

In the Gaussian case, in which the functions appearing in the exponents of the competition kernel α and the carrying capacity K are quadratic, interactions between phenotypic components generate diversity that is represented as multivariate, unimodal Gaussian equilibrium distributions of the dynamics (Eq. 6), formu-

lated in coordinates that are linear combinations of the original phenotypic axes. These distributions have a single maximum and hence represent the maintenance of standing genetic variation, but not of distinct phenotypic clusters (Fig. 1). Projections of such equilibrium distributions onto the original phenotype axes would result in unimodal distributions with positive variance of at least two, and generally of many, of the original phenotypic components.

Adding interactions between phenotypes in non-Gaussian models, in which the functions appearing in the exponents of the competition kernel α and the carrying capacity K are not quadratic, has very similar effects and can also strongly promote the maintenance of diversity. For example, replacing the competition kernel (Eq. 4) and the carrying capacity (Eq. 5) by functions with quartic exponents

$$\alpha(x_1, \ldots, x_m, y_1, \ldots, y_m) = \exp\left[-\left((x-y)\cdot A\cdot(x-y)^T\right)^2\right] \tag{9}$$

$$K(x_1,\ldots,x_m) = K_0\exp\left[-\left(x\cdot K\cdot x^T\right)^2\right] \tag{10}$$

results in qualitatively very similar effects on the maintenance of diversity as shown in Fig. 2. However, in contrast to Gaussian models, in which diversity is maintained in the form of unimodal distributions with positive variance, in the non-Gaussian model resulting from Eqs. 9 and 10, diversification induced by phenotype interactions takes the form of multimodal equilibrium distributions representing different phenotypic clusters (Fig. 3).

The message from this analysis is simple and general. Suppose there are a number of phenotypes, each of which is under both stabilizing selection and frequency-dependent selection, so that frequency dependence is too weak to induce the maintenance of diversity along any of the phenotypic components in isolation. Then any interaction between phenotypes (that is, any departure from multiplicative determination of ecological properties) strongly increases the propensity for diversification. In essence, this is a consequence of the mathematics of simultaneous diagonalization of quadratic forms. When two quadratic forms with identical diagonal elements and arbitrary off-diagonal elements of comparable scale are simultaneously diagonalized so that one of the forms becomes the identity matrix, then the other quadratic form will have some diagonal elements that are larger than 1 and some that are smaller than 1. The sign of the off-diagonal elements, and hence the sign of the phenotypic interactions, does not matter for this effect, and the higher the dimension of phenotype space, the stronger the effect, so that for very high-dimensional phenotype spaces, phenotypic interactions can generate diversity even if frequency dependence is very weak in each component direction. The models we used are related to competition models with multidimensional resources (*24*), and the results are reminiscent of earlier findings that adding a spatial dimension to models of frequency-dependent selection can enhance the maintenance of diversity (*25*, *26*). Our results remain valid if the model given by Eq. 6 is altered to include mutations and/or sexual reproduction [for example, based on (*20*)]. In that case, the maintenance of substantial variation also requires frequency dependence, and hence phenotypic interactions in high-dimensional phenotype spaces also promote diversity. However, in sexual populations, the generation of diversity as multimodal phenotype distributions requires assortative mating (*20*). We have derived our results for classical competition models, but in essence the analysis only depends on the relative local curvatures at the maxima of the carrying capacity and the competition kernel and should therefore extend to any functions having a nondegenerate Taylor expansion at those maxima. It has been argued that competition models of the type considered here may be locally representative of a large class of models (*27*), and we conjecture that the effects observed here occur whenever frequency-dependent selection on high-dimensional phenotypes is determined by complex interactions between phenotypic components. This is different from the classical explanation for the maintenance of variation in continuous characters determined by multiple loci (*10*), which is based on mutation-selection balance, and which has been challenged repeatedly (*7*, *28*, *29*).

In real systems, phenotype space is often very high-dimensional, and interactions between phenotypic components in determining ecological properties must be ubiquitous. Therefore, the strength of frequency-dependent selection along each phenotypic component may be much less important for the maintenance of diversity than previously thought, and the conditions for the origin of diversity may be much more generally satisfied. According to our models, such diversity should often manifest itself through segregation along a composite direction in phenotype space by simultaneous and coordinated diversification of two or more phenotypic traits. The splitting of bacterial populations into subpopulations with anticorrelated metabolic networks (*30*) and of insect species into different host races with many correlated trait differentiations (*31*, *32*) are potential examples of such diversification in non-separable phenotype spaces. Our theory may help explain the extraordinary amounts of diversity found in marine microbial ecosystems (*33*–*35*) and in some microbial evolution experiments (*36*). Indeed, we think that microbes are good candidates for experimental tests of our models, as it is technically feasible to manipulate many metabolic pathways, such as those for resource acquisition and the secretion of toxins and other metabolites. In particular, it would be interesting to test whether at the genetic level, pathways controlling different traits become co-regulated to enable inheritability of composite, diversifying traits. In conclusion, if the complexity of high-dimensional phenotypes with interacting components is taken into account, the origin and maintenance of diversity may not be such a riddle after all.

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Supporting Online Material

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References

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Stoichiometry and Architecture of Active DNA Replication Machinery in *Escherichia coli*

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The multiprotein replisome complex that replicates DNA has been extensively characterized in vitro, but its composition and architecture in vivo is unknown. Using millisecond single-molecule fluorescence microscopy in living cells expressing fluorescent derivatives of replisome components, we have examined replisome stoichiometry and architecture. Active *Escherichia coli* replisomes contain three molecules of the replicative polymerase, rather than the historically accepted two. These are associated with three molecules of τ, a clamp loader component that trimerizes polymerase. Only two of the three sliding clamps are always associated with the core replisome. Single-strand binding protein has a broader spatial distribution than the core components, with 5 to 11 tetramers per replisome. This in vivo technique could provide single-molecule insight into other molecular machines

Replisomes are dynamic multiprotein machines that replicate DNA by copying the leading-strand template continuously and the lagging-strand template discontinuously In *E. coli* the replisome couples the activities of more than 11 proteins during genome replication (*1*, *2*). The DnaB helicase, loaded onto the lagging-strand template, separates the two templates that are subsequently copied by Pol III polymerase (αεθ). Pol III processivity results from binding to a sliding clamp (β) encircling duplex DNA; sliding clamps are added and removed by a clamp loader [$(\tau/\gamma)_3\delta\delta'\psi\chi$] whose τ component oligomerizes Pol III. Unwound DNA on the lagging-strand template is bound by single-strand binding protein (Ssb) tetramers that remove DNA secondary structure and protect against nucleases. Primase binds to helicase during cycles of priming and DNA synthesis on the lagging-strand template

In vitro studies of the replisome have yielded details of replisome organization and the replication mechanism but have not revealed how replication is organized within living cells. Additional copies of known replisome components may be present at replication forks, whereas additional cellular factors, absent from in vitro assays, may modify the composition of the replisome and act in DNA processing. Furthermore, the techniques used to determine stoichiometry and architecture in vitro favor strong interactions, potentially biasing estimates on numbers and interactions, and are subject to complications if any component is proteolytically sensitive. We thus investigated active replisome architecture in living cells by means of a fluorescence microscopy protocol with single-molecule sensitivity and millisecond temporal resolution.

Using fully functional fluorescent C- or N-terminal YPet derivatives of *E. coli* replisome components expressed from their endogenous promoters, we showed previously that the two spatially separable sister replisomes derived from a single initiation event at the replication origin, *oriC*, track independently along DNA (*3*). Using these and additional fusions, we analyzed 10 components of individual replisomes by "slimfield" fluorescence microscopy, which uses a compact Gaussian laser excitation field (~30 μm^2) that encompasses single cells with an excitation intensity ~100 times that of wide-field fluorescence (*4*, *5*). This imaging allows quantitative detection of single fluorescent molecules at 3-ms capture rates (Fig. 1, A and B). The high laser excitation intensity does not abolish DNA replication, as judged by a factor of 2 difference in turnover on DNA of Ssb-YPet in replicating and nonreplicating cells exposed to an excitation intensity and duration similar to that of slimfield microscopy (fig. S1), consistent with the demonstration that similar exposures do not inhibit flagellar rotation (*4*).

For estimation of stoichiometry, image frames were averaged over 90 ms to define "regions of interest" that are hotspots for localization of a given YPet fusion protein. The position, size, shape, and intensity of the spots were measured automatically for each individual image frame, generating step-like intensity traces as photobleaching occurred (Fig. 1, D and E). We measured the step spacing with the use of an edge-preserving filter (*6*, *7*) combined with Fourier spectral analysis and compared these with intensity traces from purified YPet in vitro (*8*–*10*); the in vivo steps were

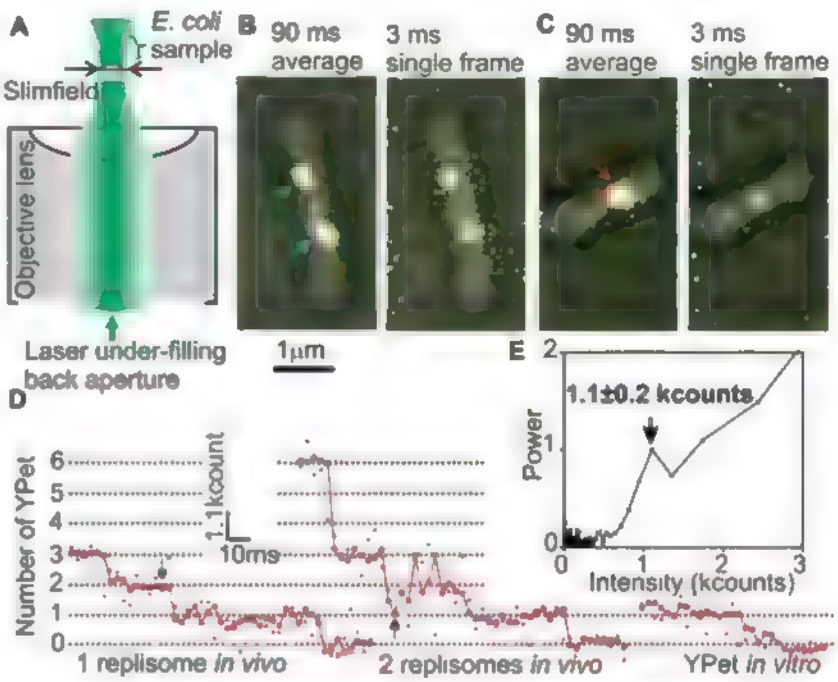

Fig. 1. Slimfield microscopy and photobleach analysis. (**A**) Slimfield schematic A laser underfills the back aperture of an objective lens, generating an intense Gaussian field at the sample large enough to image single *E. coli*. (**B** and **C**) Overlaid bright-field (gray) and 90-ms frame-averaged fluorescence images (yellow) of ε-YPet strain, arrows indicate spots with a stoichiometry of ~3 [cyan, (B)] and ~6 [red, (C)] ε-YPet molecules, with corresponding single 3-ms frames taken after 45 ms, showing that stochastic photobleaching generates different brightnesses. (**D**) Raw intensity (blue) and filtered data (red) for a putative single (left panel) and double (right panel) replisome spot with surface-immobilized YPet in vitro; arrows indicate the 45-ms point. (**E**) Fourier spectral analysis for a photobleach trace of the ε-YPet strain with mean + SD peak indicated for brightness of a single YPet.

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approximately integer multiples of the in vitro intensity of a single YPet molecule (4, 5, 8–13). Thus, intensities prior to photobleaching enabled single-molecule stoichiometry determination (5).

For most replisome components, we observed bimodal 1:2 distributions of stoichiometries, reflecting the observation that ~75% of cells contain two spatially separated replisomes, each associated with independent forks, while ~25% have sister replisomes separated by a distance smaller than the diffraction limit of our system (~250 nm) and are thus observed as a single spot (3). Lower stoichiometries were always associated with spots from cells containing two spots; cells with a single spot displayed doubled stoichiometries (Fig. 2). With the ε-YPet strain we observed a bimodal distribution with two Gaussians, peaks centered on 2.9 ± 1.0 (mean ± SD, SEM ~0.2) and 6.0 ± 1.3 molecules, consistent with a model in which a single fork contains three copies of ε, the proofreading exonuclease of the core polymerase. The Pol III catalytic subunit, α, had a bimodal distribution with peaks centered on 3.1 ± 1.1 and 5.8 ± 1.1 molecules. Similarly, the clamp loader component, τ, which also oligomerizes the polymerase, had peaks at 3.1 ± 0.8 and 5.6 ± 0.8 molecules. An essential component of the clamp loader, δ, expected to be present in one copy, had peaks at 1.0 ± 0.4 and 2.0 ± 0.4 molecules. Furthermore, we observed a stoichiometry of ~6 and ~12 molecules for DnaB (fig. S2), as expected for the hexameric helicase.

Nonessential χ and ψ, which heterodimerize, have been reported to be present at one copy per replisome because of ψ binding to γ/τ in the clamp loader (1, 14). Instead, we found a mean of ~4 copies per single replisome spot (Fig. 2); single-spot cells had ~8 molecules per spot, with a broader distribution of stoichiometries than for other low-copy components. We propose that this results from one χψ heterodimer being tethered to the clamp loader while the other χψ dimers bind available C-terminal tails of the same or different Ssb tetramers by a characterized interaction through χ (14). The intensity of ψ-YPet foci is greatly reduced when χ is absent, but χ focus intensity is unchanged when ψ is absent, supporting this hypothesis (fig. S3).

dnaX expresses comparable amounts of τ and a truncated form, γ, formed by a programmed frameshift (15); τ and γ can interchangeably be clamp loader constituents, but only τ oligomerizes Pol III (1). Our demonstration that three copies of τ are associated with the replisome suggests that γ is not associated with the single clamp loader in most replisomes. To test this, we constructed two strains: *dnaX*(γ^-), which did not express γ because the frameshift was abrogated, and *dnaX*(γ-YPet), which expressed γ-YPet. The strain that failed to express γ grew well, confirming that γ is nonessential (16), while the strain expressing γ-YPet showed fluorescent replisome-associated foci (fig. S4A). Because γ can interact with χψ, we considered whether γ might be Ssb-associated via a linking interaction

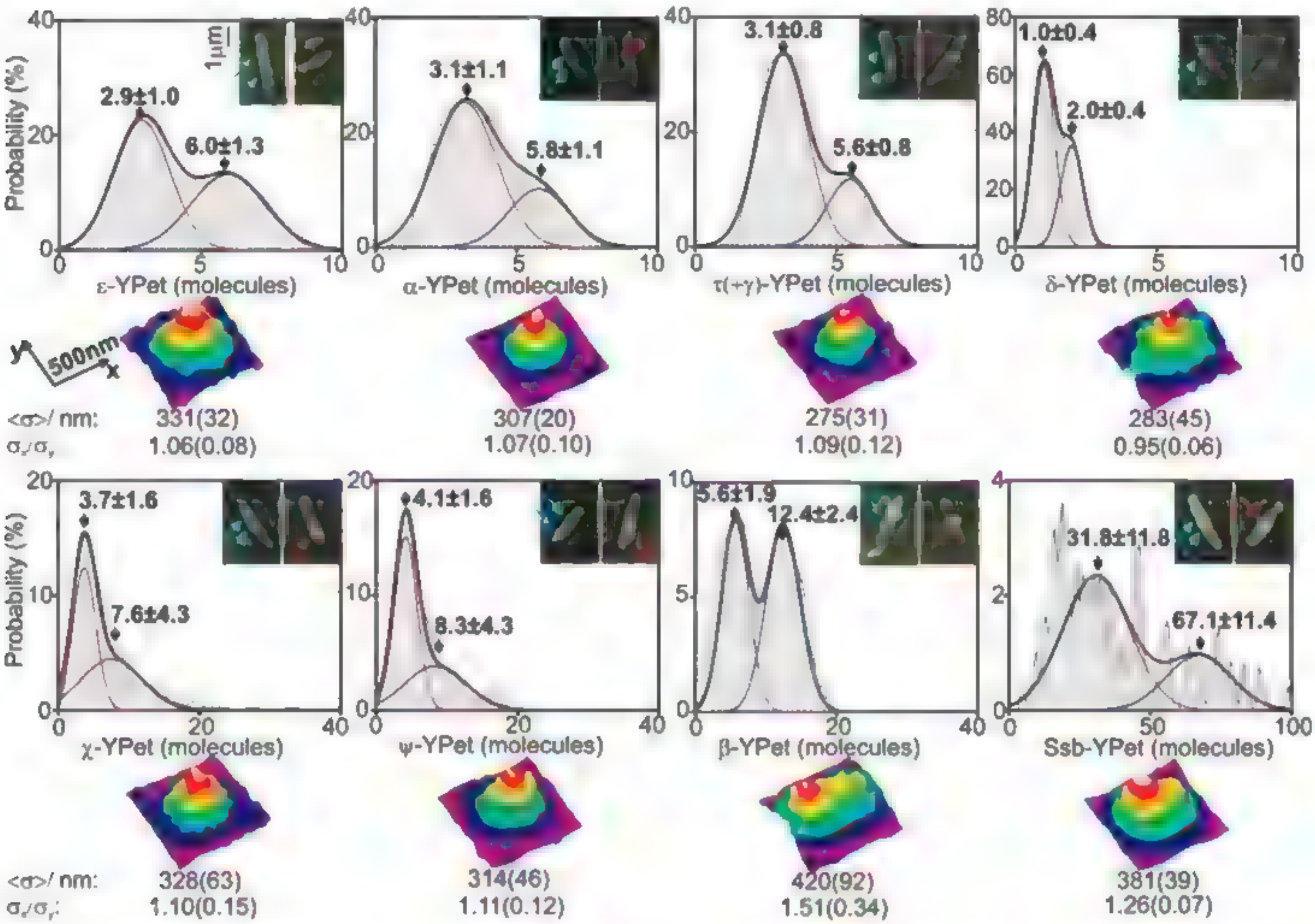


Fig. 2. Stoichiometries of replisome components and spatial distributions. Upper panels: Stoichiometry distributions per spot, using unbiased kernel density estimation for different *E. coli* strains (*N* = 27 to 51 cells in each data set); shown are two-Gaussian fits (black) with contributing single-Gaussian curves (red and blue) and mean ± SD of Gaussian peaks. Insets show examples of overlaid bright-field (gray) and single 3-ms fluorescence images (yellow) for each; arrows indicate foci in cells containing two (cyan) and one (red) replisome. Lower panels: False-color contour plots for 2D averaged spatial distributions for each strain (*N* = 42 to 151 spots in each data set). Estimates for mean FWHM ⟨σ⟩ of a symmetrical 2D Gaussian fit and the ratio σ_x/σ_y of the FWHM for the 1D Gaussian fits through the mean spot parallel to the *x* and *y* axes are indicated; SD errors are in parentheses.

with the $\chi\psi$ heterodimers not associated with the clamp loader (Fig. 3). Targeted proteolysis of degron-tagged ψ, or deletion of χ or ψ, led to a loss of replisome-associated γ-YPet foci, but not ε-YPet or τ-YPet foci; the remaining γ-YPet foci were of reduced intensity (fig. S4B). Thus, the single replicative clamp loader in each replisome contains τ but not γ, and the clamp loader–independent copies of $\chi\psi$ associated with Ssb are likely to recruit γ to Ssb in addition to acting in primase release (*17*). We propose that γ may replace τ as a clamp loader component in postreplication repair-associated events at the replication fork. Comparison of τ stoichiometry in *dnaX* and *dnaX*(γ^-) strains showed a ~30% increase when γ was absent (fig. S5), indicating that γ and τ can compete for binding to Ssb.

In contrast to the structural skeleton components of the replisome, Ssb showed a broad distribution of stoichiometries (Fig. 2) with a periodicity of ~4 molecules (fig. S6) and a mean of 31.8 ± 11.1 molecules per spot for cells containing two spots per cell, consistent with 8 ± 3 Ssb tetramers per replication fork. Single-spot cells had a stoichiometry larger by a factor of ~2, at ~70 molecules per spot. The number of Ssb molecules bound at the replication fork is expected to be proportional to the length of single-stranded DNA (ssDNA). The average stoichiometry of Ssb within replisomes approximately doubled in cells treated with hydroxyurea (*5*), as expected, because ssDNA accumulates at the fork when replication is stalled (*18*). The ssDNA associated with each Ssb tetramer is either 35 or 65 nucleotides (nt) in vitro; $(Ssb)_{35}$ forms compact filaments, whereas $(Ssb)_{65}$ forms dimers of tetramers covering 170 nt (*19*). The contribution of each binding mode in vivo is unknown. Assuming that the stretch of ssDNA at the replication fork equals the Okazaki fragment length [~650 nt at 22°C (*20*)], then the presence of $(Ssb)_{65}$ would give an occupancy of ~8 tetramers, close to our mean stoichiometry estimate for single replisome spots (Fig. 2).

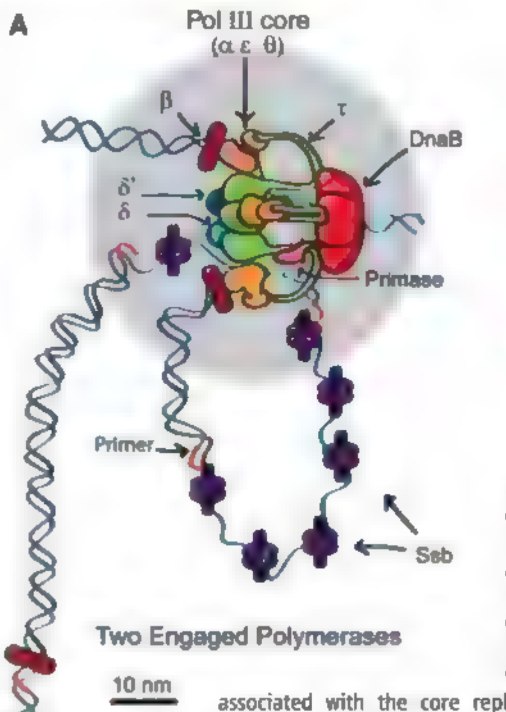
Structural investigations of replisome components suggest that their cumulative volume is contained in a sphere of maximum diameter ~50 nm (*21–24*). To investigate this, we studied the size and shape of images from each strain (Fig. 2, lower panels). Strains expressing fluorescent α, ε, τ, δ, χ, and ψ all produced spots with a circularly symmetrical shape and a mean full width at half maximum (FWHM) across the cell strains of 305 ± 30 nm (*5*). There was no significant difference from the individual FWHM measurements for each strain ($P = 0.05$, Student *t* test), but all were significantly larger than the FWHM of surface-immobilized YPet in vitro of ~250 nm (fig. S7). In contrast, β and Ssb produced spots spread further over the long axis of the cell, with Ssb foci extending up to ~200 nm; ~55% of the tetramers were present within a 50-nm diameter. Although the ~4 $\chi\psi$ heterodimers may interact with Ssb tails, we note that the spatial distribution of $\chi\psi$ is that of the core replisome–clamp loader rather than that of Ssb. Furthermore, the stoichiometry of $\chi\psi$ is much lower than that of Ssb. Taken together, these results suggest that $\chi\psi$ is associated preferentially with one or a few Ssb molecules in the vicinity of the core replisome.

The stoichiometry of the dimeric β sliding clamp was expected to be partly the result of its interaction with Pol III and the clamp loader, and partly due to association with DNA at the 3′ end of Okazaki fragments. Nonetheless, its bimodal distribution peaked at ~3 and ~6 dimers (Fig. 2), which raised the possibility that it might be continually associated with Pol III. Analysis of β-YPet spots indicated two subpopulations with different spatial intensity distributions (fig. S8). The first subgroup (~27% of spots) had circular distributions that support a scheme in which three β dimers are associated with active Pol III or with the clamp loader. In the second subgroup, the spots were more extended (circularity > 1.2), consistent with at least one of the sliding clamps being localized at a distance >50 nm from the replisome core.

Historically, the replisome has been considered to have two opposing yet coordinated polymerases connected to the rest of the replisome (*25*). Instead, we provide strong evidence for an in vivo core replisome containing three Pol IIIs associated with a clamp loader whose three copies of τ also trimerize Pol III. In a minority of replisomes, all three Pol IIIs may be associated with sliding clamps, with two being potentially simultaneously active on the lagging strand, supporting suggestions from in vitro studies of *E. coli* and phage T4 replisomes (*2*, *26*). However, the majority of replisomes appear to have only two of the polymerases associated with a sliding clamp, which suggests that the third polymerase is waiting to be loaded onto the next lagging-strand primer (Fig. 3).

We measured the number of nonreplisome Ssb tetramers to be 330 ± 105 per cell (table S1), in agreement with estimates using quantitative Western blots (*5*). Similarly, 0.5 to 5% of other replisome molecules in a cell were associated with each replisome (table S1), hence the measured stoichiometries reflect biologically relevant complexes and are not the consequence of the replisome's component being rate-limiting. The level of replisome molecules is sufficient to support more than 10 cellular replication forks associated with the chromosome, plasmids, or phage.

Slimfield microscopy provides a powerful noninvasive in vivo analytical tool that extends previous analyses of the assembly and action of molecular machines (*10*, *27*, *28*). In combination with degron-targeted proteolysis of specific proteins, it has provided unanticipated insight into replisome architecture. In combination with partial prebleaching and stochastic photoactivation and photoswitching techniques, the methodology may provide new insight into biological systems that contain substantially higher numbers of freely diffusing fluorescent proteins than were investigated here.



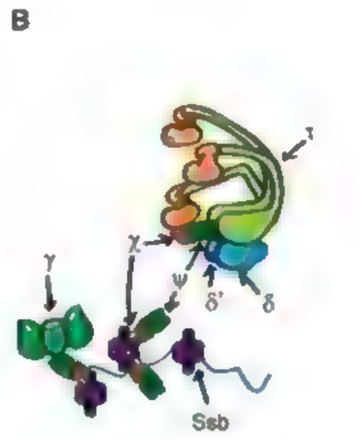


Fig. 3. Schematic model for replisome components. (**A**) Two engaged polymerases and one of the three β clamps at a distance from the core replisome (circle of diameter 50 nm shown in gray). The data indicate that ~75% of replisomes have this organization, whereas ~25% have all three β clamps associated with the core replisome and potentially associated with active Pol III. (**B**) Expanded view of clamp loader ($\tau_3\delta\delta'\psi\chi$) and three additional molecules of $\chi\psi$ interacting with Ssb tails. The $\chi\psi$ heterodimer bound to the clamp loader may also contact Ssb (*14*); γ (shown as a trimer, but the stoichiometry is unknown) then interacts with Ssb-associated $\chi\psi$.

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Supporting Online Material
www.sciencemag.org/cgi/content/full/328/5977/498/DC1
Materials and Methods
Figs. S1 to S11
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A NusE:NusG Complex Links Transcription and Translation

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Bacterial NusG is a highly conserved transcription factor that is required for most Rho activity in vivo. We show by nuclear magnetic resonance spectroscopy that *Escherichia coli* NusG carboxy-terminal domain forms a complex alternatively with Rho or with transcription factor NusE, a protein identical to 30*S* ribosomal protein S10. Because NusG amino-terminal domain contacts RNA polymerase and the NusG carboxyl-terminal domain interaction site of NusE is accessible in the ribosomal 30*S* subunit, NusG may act as a link between transcription and translation. Uncoupling of transcription and translation at the ends of bacterial operons enables transcription termination by Rho factor, and competition between ribosomal NusE and Rho for NusG helps to explain why Rho cannot terminate translated transcripts.

Escherichia coli NusG is a two-domain protein (fig. S1) (*1*) that is essential for cell viability (*2*). NusG homologs are found in all known bacteria, and the 27–amino acid NusG carboxy-terminal domain (CTD) Kyprides-Onzonis-Woese (KOW) motif is found in proteins from archaea and eukaryotes (*3–5*). A sequence highly homologous to NusG amino-terminal domain (NTD) followed by KOW motifs appears in human transcription factor hSpt5 (*6*). NusG suppresses RNA polymerase (RNAP) pausing and increases elongation rates in vitro. In vivo, it acts in concert with NusA, NusB, and NusE to promote read-through of terminators within ribosomal *rrn* operons and on the phage λ chromosome, a process that additionally requires the λ N protein (*7*). NusG activates Rho transcription termination factor in vitro and is necessary for most Rho-mediated termination events in vivo (*8*, *9*). NusG-NTD binds to RNAP and increases the rate of transcription elongation but cannot stimulate termination (*1*, *10*).

The rates of transcription and translation are correlated over a range of different growth rates (*11*), and NusG was suggested to be involved in this correlation (*12*). Thus, depletion of NusG slowed the rate of *lacZ* translation without affecting the rate of *lacZ* transcription elongation (*12*). The dual capacity of NusG to act in transcription as well as in translation is shared by the 30*S* ribosomal subunit protein NusE, which doubles as a component of some transcription elongation complexes (TECs) (*13*). As a transcription factor, NusE is loaded by NusB onto the *boxA* sequence within *nut* RNA (*14–16*) and becomes part of an antitermination complex that includes NusA, NusG, and other cellular factors (*7*, *17*). The NusB:NusE:RNA ternary complex is proposed to associate with RNAP through NusE (*7*, *18*).

Genetic evidence supports an interaction between NusG and NusE. Thus, the *nusG4* (*S163F*) mutation restores λ N antitermination in a *nusE71* (*nusEA86D*) strain (*19*). We asked whether this genetic interaction reflects a direct physical contact between the proteins. For all experiments, we used the $\mathrm{NusE}^{\Delta\mathrm{loop}}$ variant (*15*), referred to here as NusE. $\mathrm{NusE}^{\Delta\mathrm{loop}}$ is fully active for transcription, although it cannot support translation (fig. S2) (*20*), and its crystal structure is known in the NusB:NusE complex (*15*). We analyzed mixtures of NusG and the NusB:NusE complex by size exclusion chromatography. A mixture of NusB:NusE and NusG eluted earlier from the column than either NusB:NusE or NusG alone (fig. S3) (*20*), consistent with formation of a NusB:NusE:NusG complex. To confirm the interaction and to map contact surfaces, we investigated complex formation by NMR. Titration of isolated ^{15}N-labeled NusG-NTD or NusG-CTD with NusB:NusE complex caused chemical shift changes in the ^{1}H, ^{15}N-HSQC (heteronuclear single quantum coherence) nuclear magnetic resonance (NMR) spectrum of NusG-CTD but not of NusG-NTD (figs. S4 and S5). Reverse labeling (^{15}N-NusE or ^{15}N-NusB and unlabeled NusG-CTD) revealed that NusE is the recognition protein in the NusB:NusE complex (figs. S4 and S5), suggesting direct NusG-CTD:NusE interaction.

From the chemical shift changes upon titration, we could estimate the dissociation constant for the NusB:NusE:NusG-CTD (molecular mass of 32.3 kD) interaction as K_d = 50 μM (fig. S6). Comparison of secondary chemical shifts and characteristic nuclear Overhauser enhancement spectroscopy (NOESY) cross-peak patterns of NusB:NusE and NusG-CTD with the corresponding data of the NusB:NusE:NusG-CTD complex revealed no substantial conformational changes in any of the participating proteins, indicating that only minor side chain rearrangements are necessary to form the interaction surfaces (Fig.

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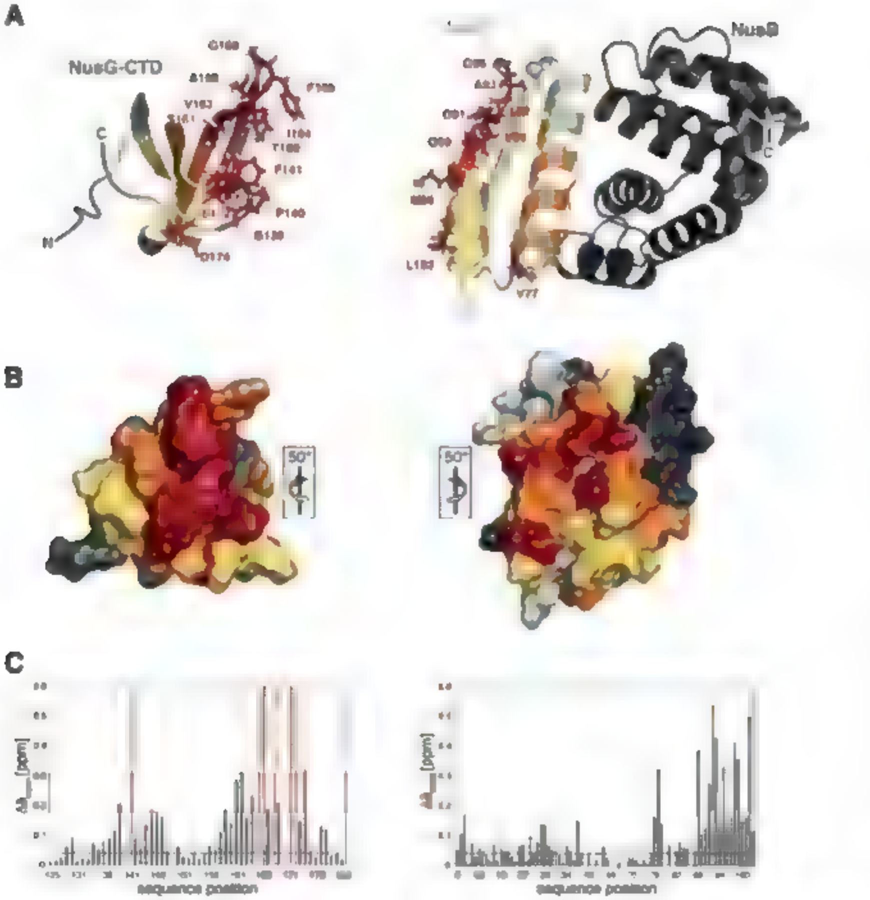

Fig. 1. (**A**) Mapping of chemical shift changes {$\Delta\delta_{norm}$ [in parts per million (ppm)] > 0.2, red; > 0.1, orange; and > 0.04, yellow} on the structures of NusG-CTD [gray, Protein Data Bank identification code (PDB ID) 2JVV (*1*)] and the NusB:NusE complex [dark gray and light gray, respectively; PDB ID 3D3B (*15*)]. Strongly affected residues are labeled (*22*) and shown as sticks. Coloring scheme is as follows: carbon, red; hydrogen, white; oxygen, red, nitrogen, blue, sulfur, yellow. The light gray sphere in NusE denotes the Cα position of S46, which in this construct replaces residues 46 to 67 of wild-type NusE (*20*). Numbering is based on the residue numbers of wild-type NusE (1 to 46 and 68 to 103). (**B**) Surface representation of the structures shown in (A). Orientations relative to (A) are indicated. (**C**) HSQC-derived chemical shift changes versus sequence position. (Left) NusG-CTD chemical shift changes on titration with NusB:NusE; (right) NusE (in the NusB:NusE complex) chemical shift changes on titration with NusG-CTD; missing residues of the NusE ribosome-binding loop are indicated by small double bars on the sequence axis (right). Dotted line, significance level of $\Delta\delta_{norm}$[ppm] = 0.04; red bars, NusG-CTD signals disappearing on complex formation.

1). Isotope-filtered NOESY spectra (fig. S7) (*21*) revealed unambiguous intermolecular contacts: NusG-I164:NusE-M88, NusG-I164:NusE-I100, NusG-T169:NusE-Q99, NusG-P140:NusE-V84, NusG-R167:NusE-V98, and NusG-E172:NusE-S101 (*22*) (Fig. 2A). Docking of the rigid domains with flexible side chains using the NOESY-derived intermolecular NOEs as distance restraints yielded a distinct conformation of the complex without any violation of the restraints (fig. S8). The NusE-binding region on NusG-CTD is composed of loops between β strands β1 and β2, β3 and β4, and residues from β strand β4. Hydrophobic amino acids P140, F141, F144, I164, and F165 show close contacts to hydrophobic residues of NusE. NusG-R167 is very close to NusE-D87, and NusG-F165 at the tip of the loop between β strands β3 and β4 is buried deeply in a hydrophobic pocket on NusE (Fig. 2, B and C). The NusE hydrophobic pocket is composed of residues from helix α2 and the carboxy-terminal β-strand β4. There were no significant effects on resonances of NusB in the NMR spectra of the NusB:NusE complex upon binding of NusG-CTD. These data together with mapping of the chemical shift changes on the sequences and the known three-dimensional structures (Fig. 1) show that the NusE-binding interface is opposite to the NusB:NusE interaction region, in proximity to the ribosome-anchoring flexible loop, R46 to T67 (fig. S2).

NusE residues M88 and D97 and NusG residues P140, F165, and R167 in the NusE:NusG-CTD interface are highly conserved among different bacteria (fig. S9), underscoring the importance of this interaction for bacterial viability. Although F165 was proposed to be required for an intramolecular NTD-CTD domain interaction in *Aquifex aeolicus* NusG (*23*), the NusE:NusG-CTD complex structure reveals that F165D or F165T mutations disturb the NusE:NusG-CTD interface.

Coregulation of transcription and translation was initially identified within the attenuation system that controls expression of amino acid biosynthetic operons (*24*), and polarity was shown

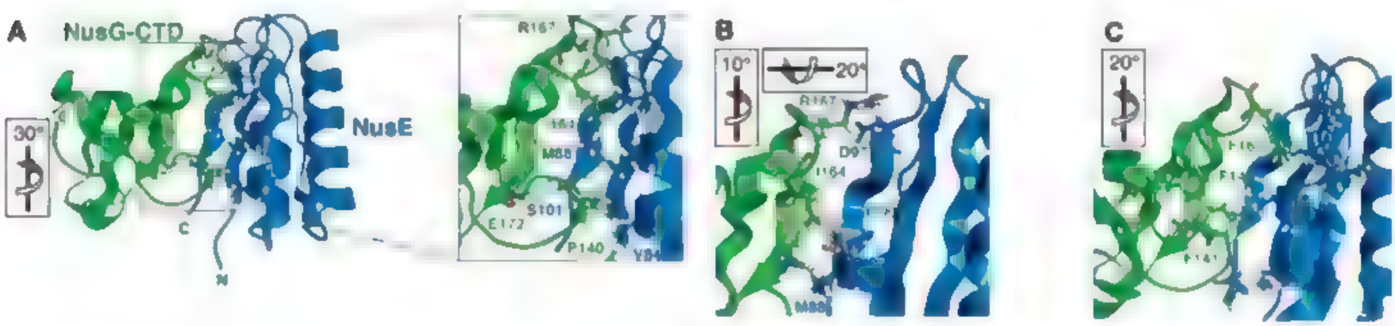

Fig. 2. (**A**) Experimental basis for the structure determination of the NusE:NusG-CTD complex. For clarity, NusB was omitted. Carbon, marine (NusE) and green (NusG); hydrogen, white; oxygen, red; nitrogen, blue; and sulfur, yellow. Black lines represent unambiguously assigned NOEs between NusG-R167-Hδ:NusE-V98-Hγ, NusG-I164-Hδ:NusE-M88-Hϵ, NusG-E172-Hβ:NusE-S101-Hβ, and NusG-P140-Hα:NusE-V84-Hβ. These intermolecular NOEs allowed unambiguous determination of the relative orientation of the two proteins by rigid body minimization. (**B**) Possible interactions in the NusE:NusG-CTD interface between negatively charged NusE-D97 and positively charged NusG-R167. NusG-I164 is sandwiched by the hydrophobic side chains of NusE-M88 and NusE-I100. (**C**) NusG-F165 and NusG-F141 bind to a NusE hydrophobic pocket. NusG-F144 is in close proximity to the interaction site and possibly participates indirectly in this interaction. Several NusE hydrophobic side chains are close to NusG phenylalanine residues. The orientation relative to Fig. 1A is indicated.

to be the result of premature Rho-dependent transcription termination induced by a translation-terminating mutation (25). The reported correlation between the rates of transcription and translation of the *infB* and *lacZ* genes, however, implies a direct linkage between the two processes (11). The interaction surface of NusE with NusG (~1100 Å^2) is still accessible when NusE forms part of the 30*S* ribosomal subunit (Fig. 3A). Thus, NusE could mediate simultaneous formation of a NusG-NTD:RNAP complex and a NusG-CTD:ribosome complex (Fig. 3B). This analysis suggests direct physical coupling of transcription and translation via NusG (Fig. 3C), a notion that is supported by the observation that NusG depletion decreases translation elongation rates (12).

We next investigated whether the physical coupling of transcription and translation via NusG interferes with the known Rho-related functions of NusG (8, 9). HSQC titrations of ^{15}N-NusG-NTD or ^{15}N-NusG-CTD with Rho showed a nearly complete loss of signals for NusG-CTD but no effect for NusG-NTD (fig. S10). The resonances of NusG-CTD are broadened beyond detection by the dramatic increase of the rotational correlation time on NusG-CTD:Rho complex formation (molecular mass of NusG-CTD is 6.9 kD; molecular mass upon addition of Rho hexamer is 288.9 kD). Thus, Rho binds to NusG-CTD but not to NusG-NTD. Signals of residues from the highly flexible N terminus of NusG-CTD [R123, K125, and T126 (Fig. 4A)] could be observed in the presence of Rho, suggesting that

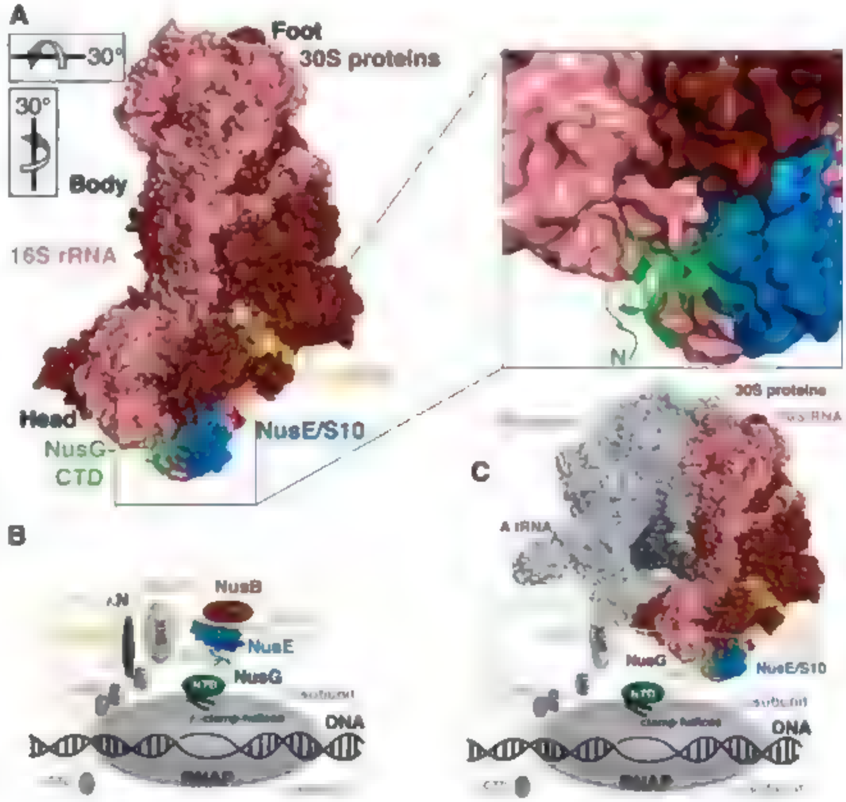

Fig. 3. (**A**) Possible interaction between NusG and NusE/S10 in the 30*S* ribosomal subunit. The NusE (marine) NusG-CTD (green) heterodimer was aligned to the structure of the *E. coli* 30*S* ribosomal subunit (ribosomal proteins, brown; 16*S* rRNA, rose). Landmark features of the 30*S* subunit (head, body, foot) are labeled. S10 is part of the head region of the 30*S* subunit in close proximity to the entrance site of the mRNA. The path of the mRNA is shown in gold. The orientation relative to Fig. 1A is shown. (**B**) Schematic representation of the assembly of the λ N–mediated antitermination complex (20). NusA domains AR1 (acidic repeat 1), AR2 (acidic repeat 2), and SKK (S1-KH1-KH2) are in light gray; RNAP αCTD, gray; *boxA*, *boxB*, and spacer region of *nut* RNA, gold; λ N, dark gray; NusB, brown; NusE, marine; NusG-CTD, green; NusG-NTD, dark green; and β′-clamp helices of the RNAP, black. (**C**) Model of the physical coupling between transcription and translation. Coloring as in (A) and (B); the 50*S* ribosomal subunit is shown in light gray and the A-site tRNA in dark gray. NusG links RNAP and the ribosome so that efficient and fast translation of the nascent mRNA can occur. Coordinates for the complete 70*S* ribosome, the mRNA, and the A-site tRNA were kindly provided by T. M. Schmeing and V. Ramakrishnan, Medical Research Council, Cambridge, United Kingdom (30).

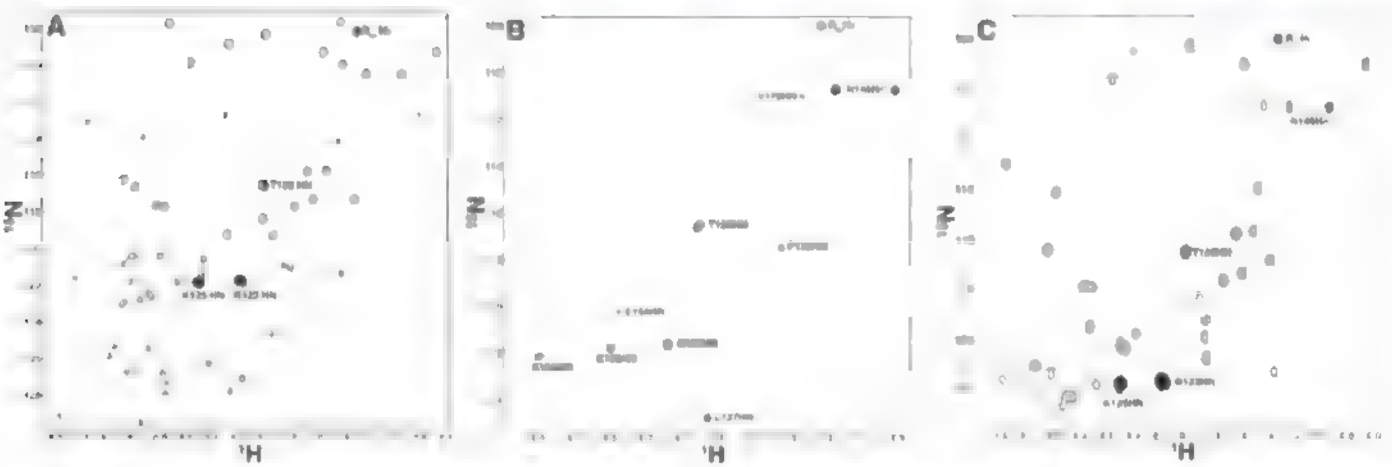

Fig. 4. (**A**) ^{1}H, ^{15}N HSQC spectra of ^{15}N-NusG-CTD titrated with Rho. Spectrum of free NusG-CTD, gray, and with an additional equivalent of Rho, black. All gray signals disappeared after Rho addition, and the remaining signals (black) are part of the spacer region between the NusG domains. (**B**) ^{1}H, ^{15}N HSQC spectra of a displacement titration of a 1:1 of ^{15}N-NusG-CTD:Rho complex (gray) with NusB:NusE. Addition of 20 equivalents of NusB:NusE, black. All newly appearing signals either belong to the spacer and the C terminus of NusG or are on the side of the spacer region pointing away from the interaction surface (E154 and N145). (**C**) ^{1}H, ^{15}N HSQC spectra of a displacement titration of a 1:1 ^{15}N-NusG-CTD:NusB:NusE complex (gray) with Rho. Addition of one equivalent of Rho, black. The resulting spectrum is identical to the spectrum observed with the NusG-CTD:Rho complex [part (A) of this figure].

they are located at the surface of the complex and do not contribute to binding. These residues are part of the linker region between NusG-CTD and NusG-NTD in full-length NusG, and their high flexibility combined with their absence from the NusG-NTD:Rho binding interface indicates that NusG-NTD remains flexibly linked to NusG-CTD in the complex with Rho. Indeed, all detectable signals of full-length ^{15}N-NusG after addition of Rho could be assigned exclusively to residues of NusG-NTD and the linker region. HSQC displacement experiments show the NusG-CTD:Rho and the NusG-CTD:NusE interactions to be mutually exclusive (Fig. 4, B and C).

Chromatin immunoprecipitation (ChIP) chip analysis indicates that Rho collocates with elongating RNAP soon after transcription initiation (*26*, *27*). How Rho is recruited to the TEC is not clear. Nevertheless, termination does not occur until transcription reaches the operon terminus. Our findings suggest a straightforward explanation for this delay in termination. We suggest that during coupled transcription-translation NusG-CTD is bound to ribosomal NusE and is therefore unavailable for binding to Rho. Release of ribosomes at the ends of operons frees the NusG-CTD to interact with and stimulate Rho. This mechanism may complement the occlusion of RNA to Rho by translating ribosomes.

The different relative affinities of NusG for NusB:NusE-CTD (K_d = 50 μM) and for Rho [K_d = 12 nM (*28*)] as reflected in the displacement experiments (Fig. 4) appear to argue against the above model. However, NusE:NusG-CTD interaction takes place within a complex with TEC that includes many other factors. Other interactions with the TEC may additionally lower the NusE:NusG-CTD K_d. For example, during processive antitermination NusB:NusE binds *boxA* RNA (*14*–*16*), linking these factors with RNAP and enhancing the overall stability of the antitermination complex. Consistent with the idea that the NusE:NusG interaction is stabilized on RNAP, we found that overproduction of NusG-CTD in wild-type *E. coli* is not toxic, suggesting that it does not efficiently compete with wild-type NusG for binding to TEC (*1*). In contrast, NusG-CTD did compete with a NusG mutant with reduced affinity for NusE. Thus, overexpression of NusG-CTD was lethal in a *nusGF165A* mutant strain, in which a key NusE interface residue on NusG is altered. We suggest that NusG-CTD titrates isolated NusE and/or ribosome-bound NusE in the mutant cells.

Lastly, our data also explain the puzzling observation that ribosome-bound NusE still supports antitermination (*29*). According to our model, this activity entails RNAP-ribosome coupling through NusG.

References and Notes

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22. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.
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Cooperation Between Translating Ribosomes and RNA Polymerase in Transcription Elongation

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During transcription of protein-coding genes, bacterial RNA polymerase (RNAP) is closely followed by a ribosome that translates the newly synthesized transcript. Our in vivo measurements show that the overall elongation rate of transcription is tightly controlled by the rate of translation. Acceleration and deceleration of a ribosome result in corresponding changes in the speed of RNAP. Moreover, we found an inverse correlation between the number of rare codons in a gene, which delay ribosome progression, and the rate of transcription. The stimulating effect of a ribosome on RNAP is achieved by preventing its spontaneous backtracking, which enhances the pace and also facilitates readthrough of roadblocks in vivo. Such a cooperative mechanism ensures that the transcriptional yield is always adjusted to translational needs at different genes and under various growth conditions.

In contrast to eukaryotes, where translation and transcription take place in different cellular compartments, in bacteria, the two principal events of gene expression are coupled in time and space. The majority of bacterial genes initiate translation soon after the ribosome-binding site (RBS) has emerged from the RNA exit channel of RNA polymerase (RNAP). Although translation-transcription coupling has been known for decades, its function was ascribed only in specific cases of transcription attenuation and polarity (*1*). When a ribosome slows down owing to, for example, amino acid deficiency, the growing gap between moving RNAP and lagging ribosome provides the termination factor Rho with access to the nascent RNA, which results in premature termination of downstream genes—a phenomenon known as the polarity effect (*2*). The ribosome can also be responsible for early transcription termination at certain metabolic operons, by allowing the formation of an intrinsic termination hairpin in the leader RNA sequences that leads to transcription attenuation (*3*). Notably, both attenuation and polarity occur when the ribosome and

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RNAP are physically separated. In each case, the effect of a ribosome on RNAP is indirect; it is mediated by either Rho factor or RNA secondary structures. In contrast, we found that for most of the coding region, the first trailing ribosome directly assists RNAP during elongation. Such cooperation between the two macromolecules explains the precise match of translational and transcriptional rates under various growth conditions (Table 1).

To measure the overall transcription elongation rate in vivo, we used a plasmid carrying the isopropyl-β-D-thiogalactopyranoside (IPTG)–inducible version of the A1 promoter of bacteriophage T7 fused to the *lacZ* reporter gene (*4*) (Fig. 1A). To calculate the elongation rate, the *Escherichia coli* culture was induced with IPTG, and the time that elapsed between the appearance of a specific hybridization signal from probes complementary to the 5′ and 3′ segments of the *lacZ* transcript was determined by dot-blot hybridization (Fig. 1 and fig. S1) (*5, 6*). Although the absolute values of the hybridization signal may vary depending on factors such as Rho termination, RNA stability, or rate of transcription initiation, the timing for the linear signal increase between the two probes depends only on RNAP speed. This setup therefore allows an accurate and unbiased determination of the elongation rate in vivo (*5, 6*). In parallel, we measured the translation elongation rate by monitoring the induction lag for β-galactosidase synthesis (fig. S2) (*7*). We first investigated the effect of the antibiotic chloramphenicol (Cm), a specific inhibitor of translation elongation, on the transcription elongation rate. Cm was added to exponentially growing cells at 1 μg/ml, a concentration that had only a mild inhibitory effect on bacterial growth. In the absence of Cm, the transcription elongation rate was determined to be 42 nucleotides (nt) per second under specified growth conditions, matching a translation elongation rate of 14 amino acids per second (Table 1 and fig. S2). However, Cm reduced the transcription elongation rate to 27 nt/s (Fig. 1B), which matched a reduced translation rate of nine amino acids per s (Table 1 and fig. S2). This result suggests that the ribosome controls the rate of RNAP propagation.

To provide further support for this conclusion and to rule out any potential indirect effect of Cm on transcription, we took advantage of a bacterial strain carrying a chromosomal mutation in the *rpsL* gene that renders the ribosome inherently slow (*4, 8*). It is advantageous that the slow translation phenotype of this mutant (CH184 cells) can be partially recovered by the antibiotic streptomycin (Sm), which also restores the growth rate of the mutant strain (*8*). Indeed, our β-galactosidase measurements indicate that, without Sm, the translation elongation rate of CH184 was 6 amino acids per s and, in the presence of 100 μg/ml Sm, 10 amino acids per s (Table 1 and fig. S2), results that are consistent with a previous study (*8*). The speed of transcription elongation in CH184 was remarkably slow (only 19 nt/s), but accelerated to 30 nt/s when Sm was added (Fig. 1C), which perfectly matched the translation elongation rates with and without Sm (Table 1). The opposite effect of translation antibiotics (Cm and Sm) on transcription elongation demonstrates a strong reliance of RNAP speed on that of a ribosome.

Codon usage affects the rate of translation in bacteria and other organisms (*9*–*11*). Rare codons, which pair to less-abundant transfer RNA isoacceptors, delay the progression of a ribosome and often compromise protein expression (*12*–*14*). If the transcriptional rate relies so heavily on translation, the codon-reading program encoded by each individual gene should determine the speed of RNAP. To test this hypothesis, we compared the rates of transcription elongation at several genes with different rare codon frequency (*4*). The *E. coli* genes *rplB* and *tufA* have a relatively small number of rare codons (Table 2 and fig. S3). In contrast, a foreign gene (*srb4*) that encodes a subunit of the yeast Mediator is characterized by a high frequency of rare codons (Table 2 and fig. S3). Open reading frames of the *rplB*-*tufA* fusion and *srb4*, which are the same length (2 kb), were inserted upstream of *lacZ* in the same test vector used in our previous experiments (Fig. 1D). Remarkably, transcription of *rplB*-*tufA* matched its fast translation rate and was more than 1.5 times as fast as that of *srb4* (Fig. 1D and Table 2). Moreover, genes carrying an intermediate number of rare codons (*lacZ* and *infB*) predictably displayed intermediate rates of transcription (Table 2). Thus, codon usage is a key determinant of transcription rate.

Previously, we showed that the rate of transcription elongation depends on the efficiency of initiation as determined by promoter strength (*5, 15*). The mechanism underlying this phenomenon was explained by the cumulative anti-backtracking effect of trailing elongation complexes (ECs) on the leading EC (fig. S4). Backtracking or spontaneous reverse sliding of the EC along DNA and RNA occurs frequently in vitro and usually determines the overall elongation rate (*5, 15*). During backtracking, the 3′ end of RNA is disengaged from the RNAP catalytic site, which causes pausing or permanent EC inactivation (*16, 17*). The leading backtracked ECs in vitro can be rescued by trailing ECs that push them forward (*5, 15*). The trailing ribosome could similarly control the rate of transcription by "pushing" backtracked ECs forward (fig. S4).

To test this hypothesis, we developed an assay in which the effect of a ribosome on RNAP backtracking could be directly monitored in vivo (*4*). We constructed a set of plasmids in which RNAP initiated from a constitutive promoter is halted at a downstream site by the *lac* repressor bound to its operator motif (Fig. 2A). Previously, we showed that RNAP backtracks when it collides with the repressor in vitro and in vivo, which restricts its ability to readthrough the roadblock (*15*). To monitor the changes in positioning of the blocked EC in response to translation, we performed in situ footprinting of the transcription bubble with the single strand–specific probe, chloroacetaldehyde (CAA) (Fig. 2B) (*15*). The plasmids were designed so that the repressor halted either two ECs transcribing in tandem (p2EC) or only one isolated EC (p1EC) (Fig. 2). In the latter case, the trp terminator was placed between the promoter and the *lac* repressor-binding site to completely terminate the trailing EC upon stalling (*15*). A derivative of p1EC (p^{RBS}1EC) was also made, which contained the strong ribosome-binding site (RBS) derived from gene 10 of bacteriophage T7 positioned 120 nt upstream of the *lac* repressor-binding site (Fig. 2A). Analysis of CAA modifications on the nontemplate strand of p2EC and p1EC revealed two ECs (nos. 1 and 2) and one EC (no. 1) between the promoter and the repressor,

Table 1. Overall transcription elongation rates match that of translation under various growth conditions. MG1655 (wild type) and CH184 (*rpsL*[SmP]) were grown in Luria broth to the exponential phase ($OD_{600} \approx 0.4$) before IPTG induction, unless indicated otherwise. Stationary phase, IPTG was added at $OD_{600} \approx 2.5$. Alternative carbon sources: Glycerol, cells were grown in M9 minimal media supplemented with glycerol (0.5%) and casamino acids (0.2%); αMG, cells were grown in glucose minimal media in the presence of α-methyl-glucoside, at the 15:1 glucose ratio. IPTG was added at $OD_{600} \approx 0.4$. Numbers represent averaged values from three independent experiments ($P < 0.05$), including those described in Fig. 1 and figs. S2, S5, S6, and S7. The standard error for each value in each individual experiment was less than 10%.

Strain	Growth condition	Transcription rates (nt/s)	Translation rates (amino acids per s)	Ratio of nt to amino acid
MG1655		42	14	3.0
MG1655	+ Cm	27	9	3.0
MG1655	Stationary	21	7	3.0
MG1655	Glycerol	31	10	3.1
MG1655	αMG	23	8	2.9
CH184	+ Sm	31	10	3.1
CH184		19	6	3.2
CH184	Stationary + Sm	22	7	3.1
CH184	Stationary	12	4	3.0

respectively (Fig. 2B). CAA signals from ECs 1 and 2 disappeared when IPTG was added, which demonstrated that, in each case, the *lac* repressor blocked the ECs (*15*). CAA footprinting revealed a significant difference in positioning of EC1 on each plasmid. Clearly, isolated EC1 in p1EC backtracks over a longer distance than EC1 in p^{RBS}1EC (or in p2EC), because new CAA reactive sites are detected upstream and the reactivity of the downstream margin of the footprint is strongly decreased (Fig. 2B, compare lanes 2 and 3). We conclude that similarly to the situation with trailing ECs (lane 1) (*15*), the trailing ribosome prevents backtracking of the leading EC.

Because trailing ECs help leading ECs traverse the roadblock by inhibiting backtracking (*15*), the inhibition of backtracking by a ribosome should also facilitate transcriptional readthrough. This premise was tested directly by comparing the amounts of downstream *cat* mRNA generated from p^{RBS}1EC and p1EC plasmids, with and without the translation inhibitors spectinomycin (Sp) and tetracycline (Tc) (*4*) (Fig. 3A). *Cat* message accumulation was measured by reverse-transcriptase primer extension and normalized to the plasmid-encoded β-lactamase transcript (bla) (Fig. 3B). Without RBS, only ~10% of ECs were transcribed beyond the roadblock (lane 1). However, the level of readthrough increased to 40% for RBS-containing plasmid (lane 3). Moreover, the ribosome-targeting antibiotics reversed the stimulating effect of RBS on transcriptional readthrough (lane 5). Because the space between the blocked RNAP and RBS can accommodate only one ribosome at a time, this analysis revealed direct in vivo cooperation between a single moving ribosome and a single moving RNAP in overcoming the transcriptional roadblock.

RNAP and ribosomes are two molecular motors with fundamentally different working cycles. Although both enzymes use Brownian ratchet principles in converting thermal energy into movement (*18*–*20*), translocation of a ribosome is virtually irreversible, whereas RNAP oscillates back and forth along RNA and DNA at numerous sites in vitro (*16*, *17*, *20*, *21*). Such an equilibrium between productive and nonproductive (pretranslocated or backtracking) states determines the pace of transcription elongation (*20*). Elongation factors, such as NusG or RfaH, shift the equilibrium toward the productive (posttranslocated) state. They accelerate transcription by changing the intrinsic translocation properties of RNAP (*20*, *22*). In contrast, a moving ribosome appears to control transcription "mechanically," by physically blocking backtracking (Fig. 2 and fig. S4) (*23*). Such cooperation between RNAP and a ribosome is reminiscent of trailing ECs helping leading ECs to overcome backtracking-type elongation blocks in vitro and in vivo (*5*, *15*, *24*). The cooperation effect in this case

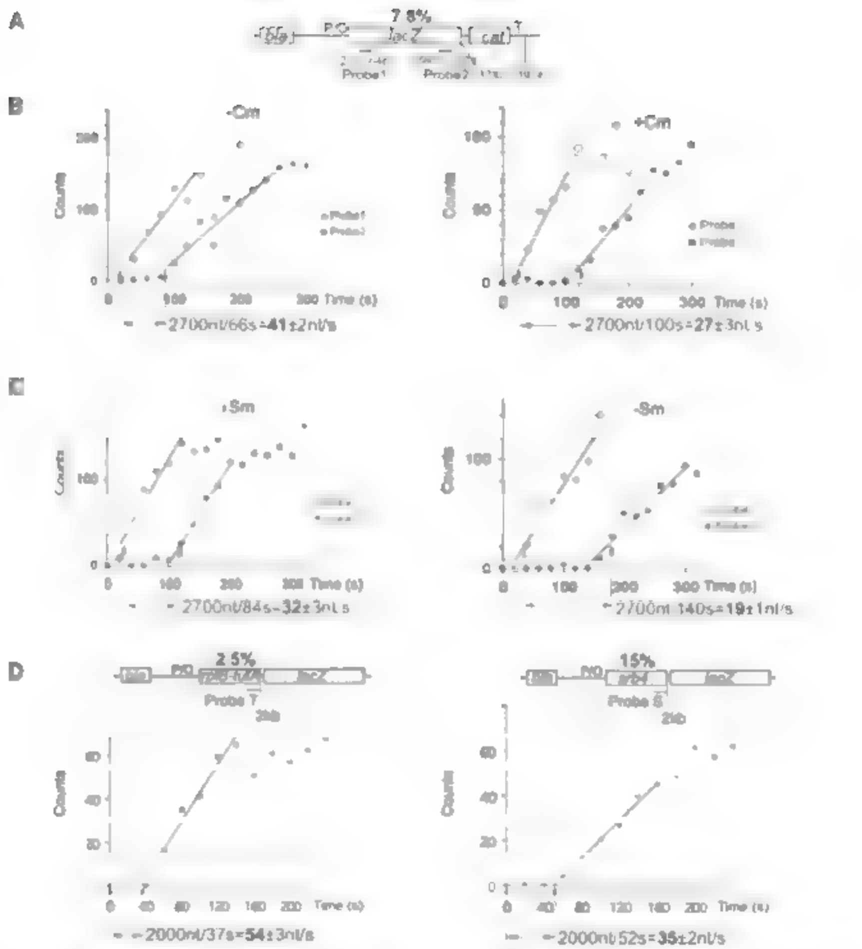

Fig. 1. The overall transcription elongation rate depends on the rate of translation. (**A**) Schematics of the test plasmid pUV12 used in (B) and (C) (*5*, *6*). White bars show genes. P/O indicates the T7A1$_{O4/O3}$ promoter-operator site; T, the terminator sequence. Lines indicate probes complementary to the *lacZ* transcript at specified positions relative to the 5′ end. The percentage of rare codons in the open reading frame (%) is indicated on top. (**B**) Effect of chloramphenicol (Cm) on transcription elongation rate. Panels display representative induction curves used to calculate the elongation rate. At time 0, IPTG was added. RNA was extracted at the indicated times after induction and used for parallel dot-blot hybridization with the early (probe 1) and late (probe 2) *lac* probes (fig. S1A). The distance between probes divided by the time of the linear increase in the hybridization signal between probes 1 and 2 (shown by arrows) gives the elongation rate. Radioactivity at time 0 (before IPTG induction) was taken as background and subtracted from all values. (**C**) Effect of the slow ribosome mutant (SmP) and streptomycin (Sm) on transcription elongation rate. Representative induction curves used to calculate the elongation rate. Corresponding dot blots of the early (probe 1) and late (probe 2) probes are shown in fig. S1B. (**D**) Rate of transcription elongation as a function of codon usage. Schematics of the test plasmids with the percentage of rare codons in the open reading frame (%) are shown on top. Two representative induction curves used to calculate the elongation rate are displayed. The amount of radioactivity in each probe was divided by the corresponding radioactivity in the *bla* probe, and the ratio is plotted against sampling time. Corresponding dot blots are shown in fig. S1C. The distance between the probe and the start of transcription divided by the time of linear increase in the hybridization signal (shown by arrows) gives the elongation rate.

Table 2. Inverse correlation between rare codon frequency and transcription elongation rates at individual genes. The percentage (%) of rare codons in each gene tested is indicated in parentheses. All numbers except those with asterisk(s) represent averaged values from three independent experiments ($P < 0.05$), including those described in Fig. 1 and fig. S2. ND, not determined.

Gene	Rare codons/length (%)	Translation rates (amino acids per s)	Transcription rates (nt/s)
rplB-tufA	16/639 (2.5)	18 ± 2*	54
infB	30/891 (3.3)	ND	45†
lacZ	80/1025 (7.8)	14	42
srb4	102/688 (15)	ND	35

*Value from (*29*). †Value from (*6*).

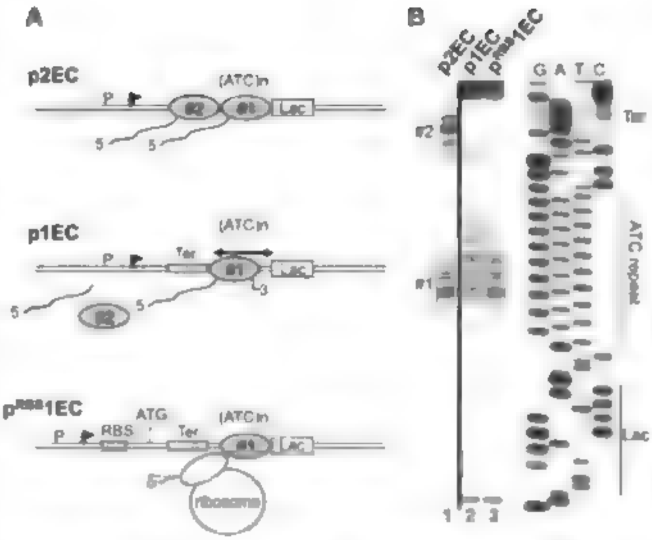

Fig. 2. The trailing ribosome inhibits RNAP backtracking. **(A)** Diagram describing p2EC, p1EC, and p^{RBS}1EC constructs and footprinting results of (B). The leading EC1 is halted by the *lac* repressor within the ATC repeated sequence (ATC)*n*. The trpT terminator (Ter) is positioned so that the trailing EC (EC2) stalled at the termination site dissociates completely. **(B)** Primer extension analyses of in situ CAA modifications of the nontemplate strand in p2EC (line 1), p1EC (line 2), and p^{RBS}1EC (line 3). The locations of the lac operator (Lac), ATC repeat, terminator (Ter), EC1, and EC2 are indicated. Red lines show the dynamic position of the EC1 transcription bubble. The presence of EC2 or trailing ribosome shifts the backtracked EC1 forward. The space between the RBS and blocked EC1 allows for only one ribosome to be engaged in translation.

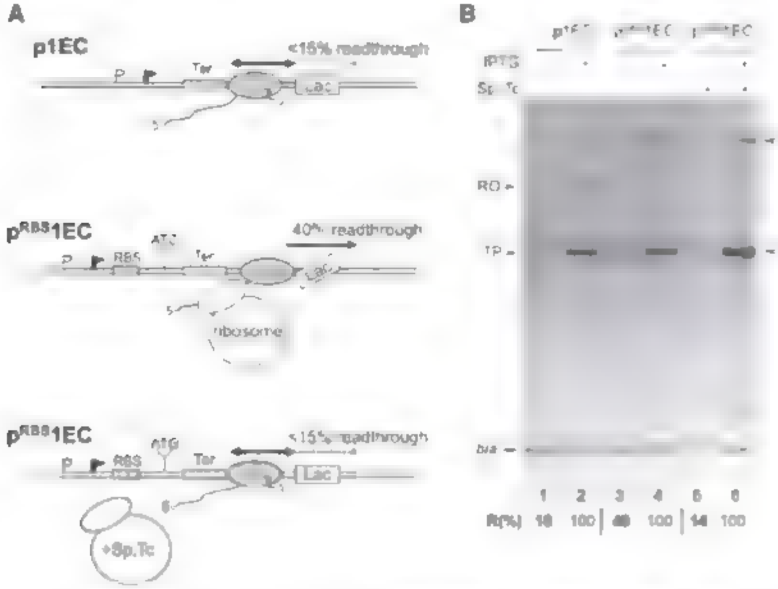

Fig. 3. Cooperation between the ribosome and leading RNAP in overcoming a transcriptional roadblock in vivo. **(A)** Diagram describing the cooperative mechanism and the results of (B). The ribosome reactivates the blocked EC (which is predominantly backtracked) by "pushing" it forward. The activated EC is now able to traverse the *lac* repressor, as soon as the latter dissociates. Inhibition of translation by antibiotics (Sp and Tc) disrupts cooperation, thereby inhibiting RNAP readthrough. **(B)** Stimulating effect of translation on transcriptional readthrough of the *lac* repressor in vivo. Autoradiogram shows the RT extension products obtained from ^{32}P primers hybridized to either *cat* or *bla* transcripts. p1EC and p^{RBS}1EC template plasmids and experimental conditions were as in Fig. 2. The ribosome inhibitors Sp and Tc were added as indicated (lanes 5 and 6). RO and TP stand for the full size (runoff) reverse transcription product and the product interrupted at the base of the trp terminator hairpin, respectively. The efficiency of transcriptional readthrough (%R) was calculated as a fraction of extension products (RO+TP) normalized to 100% readthrough in the presence of IPTG. The results are the mean from three independent experiments ($P < 0.05$).

is proportional to the promoter strength (*5*); hence, it works particularly well at highly expressed genes, such as ribosomal and other stable RNA genes. The majority of genes, however, have relatively weak promoters, which compromise RNAP cooperation at those operons. The backtracking-prone elongation by RNAP, therefore, provides a means for precise adjustment to the rate of translation by a mechanical coupling with a moving ribosome.

Indeed, we observed a perfect match between translation and transcription rates under various growth conditions, including variations in carbon sources and growth-phase transition (Table 1 and figs. S5 to S7). In the stationary phase, transcription and translation rates decelerate synchronously in "wild type" (MG1655) or "slow ribosome" (CH184) cells (figs. S6 and S7 and Table 1). Moreover, Sm accelerated both transcription and translation in the stationary growing CH184 to the levels observed in stationary growing MG1655 (fig. S7 and Table 1). Thus, the transcription elongation rate remains under tight translational control throughout bacterial growth.

In summary, the moving ribosome directly controls the rate of transcription by preventing RNAP from spontaneous backtracking. Because of such cooperation, the rate of transcription is determined by codon usage and nutrient availability sensed by the ribosome. As a result, there is a precise adjustment of transcriptional yield to translational needs under various growth conditions. Macromolecule trafficking and cooperation (fig. S4) is thus the fundamental mechanism of bacterial gene regulation and adaptation to environmental changes.

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23. In addition to preventing backtracking-type pauses, the ribosome can also suppress pausing induced by RNA secondary structures. However, the hairpin-mediated pauses are rare compared with ubiquitous backtracking-type pauses (*25*). They have been detected only within the leader sequences of a few metabolic genes (*3, 26*) and require specific sequences upstream and downstream of the pause hairpin (*27*). Usually, hairpins do not induce pausing. For example, strong termination hairpins do not pause RNAP (*28*) (fig. S8). Instead, it is a poly-T stretch of the terminator that induces backtracking-type pauses at the site of termination (*28*). Also, factors that suppress RNAP backtracking (e.g., NusG and RfaH) accelerate the overall elongation rate (*20, 22*).

(fig. S8). Therefore, it is unlikely that random secondary structures affect the overall elongation rate to the same extent as ubiquitous backtracking-type pauses in vivo.
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Dysregulated Humoral Immunity to Nontyphoidal *Salmonella* in HIV-Infected African Adults

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Nontyphoidal *Salmonellae* are a major cause of life-threatening bacteremia among HIV-infected individuals. Although cell-mediated immunity controls intracellular infection, antibodies protect against *Salmonella* bacteremia. We report that high-titer antibodies specific for *Salmonella* lipopolysaccharide (LPS) are associated with a lack of *Salmonella*-killing in HIV-infected African adults. Killing was restored by genetically shortening LPS from the target *Salmonella* or removing LPS-specific antibodies from serum. Complement-mediated killing of *Salmonella* by healthy serum is shown to be induced specifically by antibodies against outer membrane proteins. This killing is lost when excess antibody against *Salmonella* LPS is added. Thus, our study indicates that impaired immunity against nontyphoidal *Salmonella* bacteremia in HIV infection results from excess inhibitory antibodies against *Salmonella* LPS, whereas serum killing of *Salmonella* is induced by antibodies against outer membrane proteins.

The association between HIV infection and fatal disease with nontyphoidal strains of *Salmonella* (NTS) was first described at the outset of the AIDS pandemic 26 years ago (*1, 2*). This is a global problem affecting affluent countries (*3, 4*), but particularly Africa (*5–8*). The underlying mechanisms are not known. NTS, especially *Salmonella enterica* serovars Typhimurium and Enteritidis, are a major cause of invasive bacterial disease in Africa affecting young children (*5, 9*) as well as HIV-infected adults. Case fatality and recrudescence rates are high (*10*), antibiotic resistance is an increasing problem (*5*), and currently no vaccine is available. Although *Salmonellae* are facultative intracellular pathogens (*11*) and cell-mediated immunity is important for controlling infection (*12–14*), we recently demonstrated an important protective role for antibody-induced complement-mediated killing of NTS in African children (*15*). We investigated antibodies to *Salmonella* in the context of HIV infection because HIV causes extensive defects in the humoral immune system (*16–18*). Our studies reveal aberrant humoral immunity to NTS in HIV-infected African adults, characterized by a lack of bactericidal activity resulting from dysregulated antibody production, with excess immunoglobulin G (IgG) directed against *S.* Typhimurium lipopolysaccharide (LPS). We also show that antibodies against *S.* Typhimurium outer membrane proteins induce killing of NTS in HIV-uninfected African adults.

To determine whether HIV infection affects humoral immunity to NTS, we assessed in vitro killing of two invasive Malawian *S.* Typhimurium isolates by sera from Malawian adults (*19*). Isolate A23753 was killed by all sera from HIV-uninfected adults, with a $\log_{10}$ kill at 180 min of ≥0.9 (designated "normal kill") (Fig. 1A), and all effected a 3.0 $\log_{10}$ kill of A19520 by 45 min (Fig. 1B). In contrast, there was considerable variation in the ability of sera from HIV-infected adults to kill both isolates. Twenty-eight percent of sera failed to effect a 0.9 $\log_{10}$ kill of A23753 by 180 min (Fig. 1C), and 59% failed to produce a 3.0 $\log_{10}$ kill of A19520 by 45 min (Fig. 1D). All sera had normal total and alternative pathway hemolytic complement activity (table S1), excluding complement degradation or impaired synthesis as reasons for impaired killing. HIV targets $CD4^+$ T lymphocytes, and lowered blood $CD4^+$ lymphocyte numbers (CD4 counts) are associated with increased susceptibility to NTS bacteremia (*20*). CD4 counts of HIV-infected people with impaired serum killing of A23753 were lower than those with normal killing ($P = 0.05$) (fig. S1).

Next, IgG binding to *S.* Typhimurium A23753 was measured in all sera to determine whether a lack of antibody was the reason for impaired *Salmonella* killing. *S.* Typhimurium–specific IgG was present in all sera, and, paradoxically, IgG titer positively correlated with impaired *Salmonella*-killing by HIV-infected sera ($P = 0.002$) (Fig. 1, E and F). *S.* Enteritidis D24954-specific IgG was also present in all sera and positively correlated with *S.* Typhimurium IgG titer for HIV-uninfected and -infected sera (fig. S2). Some impairment of killing of *S.* Enteritidis D24954 was observed with a subset of HIV-infected sera that could not kill *S.* Typhimurium D23580. *S.* Enteritidis IgG titer correlated with impaired killing of *S.* Enteritidis (fig. S3).

In case *Salmonella*-specific antibody in HIV-infected sera could not activate complement, we measured deposition on A23753 of C5b-9 membrane attack complex (MAC), the final effector of complement-mediated bactericidal activity. MAC deposition was detected for all sera and strongly correlated with *Salmonella*-specific IgG titer for HIV-infected and -uninfected sera (Fig. 1, G and H). We also detected IgG binding and C3 complement deposition for HIV-infected and -uninfected sera by confocal microscopy (fig. S4). This indicates that a failure to deposit complement is not responsible for a lack of *Salmonella*-killing by HIV-infected serum.

Killing of *Salmonella* A23753 was impaired when different proportions of HIV-infected sera that could not kill *Salmonella* were mixed with HIV-uninfected serum (Fig. 2A). For some HIV-infected sera, this impairment was observed with one part HIV-infected serum to nine parts con-

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trol serum. Thus, an inhibitor in HIV-infected serum blocks killing. The inhibitory factor was found to be between 100 and 300 kD (Fig. 2, B and C). We tested whether this was an antibody, because IgG is approximately 160 kD. Total IgG at 10 g/liter extracted from inhibitory HIV-infected sera blocked killing of *S.* Typhimurium D23580 and D19774 by control sera (Fig. 2, D and E). Conversely, IgG from HIV-uninfected sera had no effect on killing.

We then tested whether inhibition results from excess total serum Ig, because hypergammaglobulinemia is a well-recognized feature of HIV infection (*16*, *17*). Although higher total IgG titers were present in HIV-infected as compared with -uninfected sera ($P < 0.0001$), there was only a small, yet significant correlation between total serum IgG and IgA, but not IgM, and impaired killing of *S.* Typhimurium (fig. S5). This suggests that inhibitory IgG binds specific targets on *S.* Typhimurium. We hypothesized that antibody-targeting structures away from the bacterial membrane might prevent killing. NTS are surrounded by LPS with long polysaccharide side chains (O-antigen) extending from the outer membrane along with flagella (consisting of flagellin, which is the H-antigen) (*21*). LPS and flagellin are highly immunogenic (*22*). We previously showed that the O-antigen of invasive African *S.* Typhimurium protects against complement-mediated killing in the absence of antibody (*15*). Earlier studies found that MAC deposited on LPS of *S.* Minnesota does not insert into the bacterial membrane (*23*), and rabbit LPS IgG can inhibit the bactericidal effect of bovine serum on *S.* Typhimurium (*24*). These considerations led us to test whether LPS and flagellin are targets of inhibitory IgG.

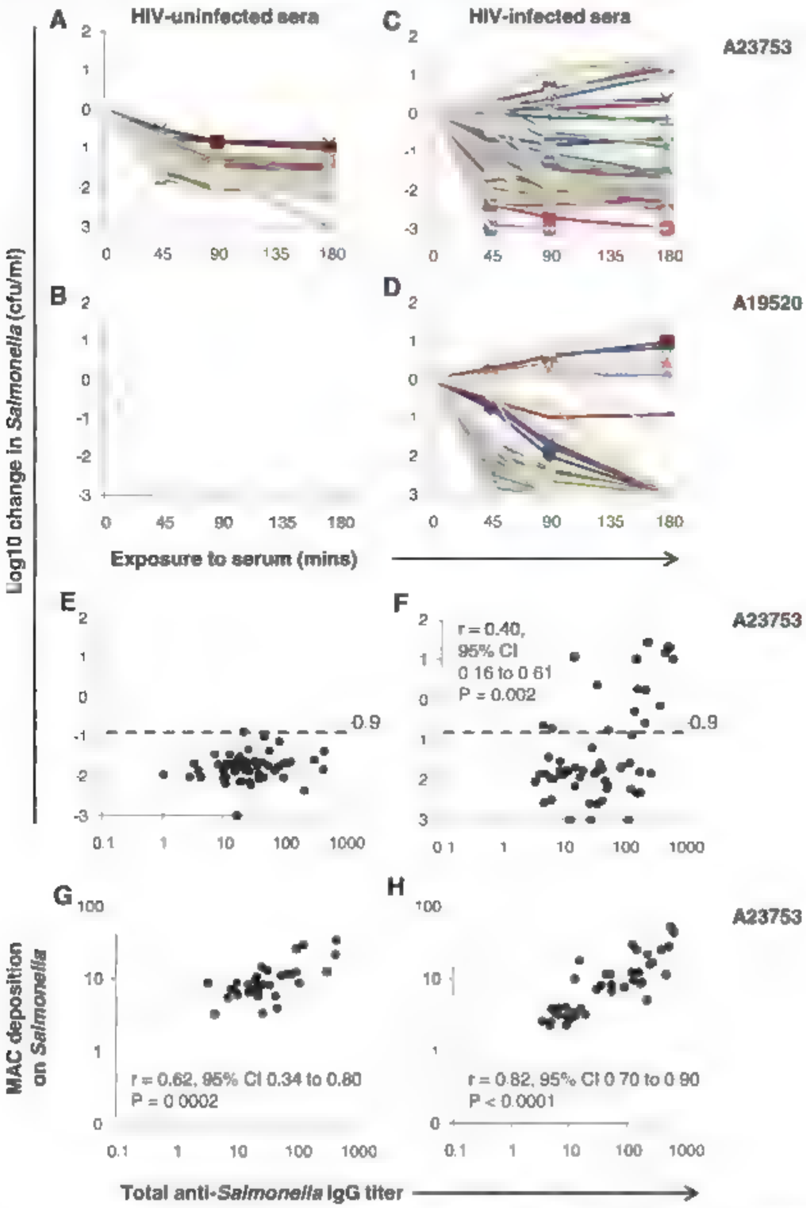

Fig. 1. Dysregulated humoral immunity to NTS in HIV infection. Killing of (**A** and **C**) *S.* Typhimurium A23753 and (**B** and **D**) serum-sensitive *S.* Typhimurium A19520 by sera at 45, 90, and 180 min. Negative values correspond with a decrease in viable *Salmonellae* as compared with the initial concentration. (**E** and **F**) Serum titers of *Salmonella* A23753 IgG compared with killing of *S.* Typhimurium A23753 at 180 min and (**G** and **H**) C5b-9 MAC deposition on A23753. CI, confidence interval. (A), (B), (E), and (G) Sera from HIV-uninfected Africans ($n = 58$). (C), (D), (F), and (H) Sera from HIV-infected Africans ($n = 58$). Each line or point represents data for serum from one individual. All lines are superimposed in (B). The horizontal dashed line in (E) and (F) indicates the threshold for impaired killing of *S.* Typhimurium A23753 (-0.9 $\log_{10}$ change in *Salmonellae* colony-forming units per milliliter).

S. Typhimurium LPS IgG titers were selectively elevated in HIV-infected compared with -uninfected sera ($P < 0.002$) (Fig. 3, A and B), whereas flagellin-specific IgG titers were comparable (fig. S6). Impaired *Salmonella*-killing in HIV-infected sera correlated with LPS IgG titer ($P = 0.0002$) but not with flagellin IgG titer. We confirmed the correlation between LPS IgG and impairment of *Salmonella*-killing by measuring LPS IgG in a subset of HIV-infected and -uninfected sera by fluorescent-bead–based immunoassay (fig. S7). These results are consistent with LPS IgG being the key inhibitor. Median IgM titers to LPS [as previously reported (*25*)] and flagellin were respectively higher or not significantly different in HIV-uninfected as compared with HIV-infected sera (fig. S8), arguing against a role for IgM in the inhibition of *Salmonella*-killing.

To test further whether LPS IgG inhibits *Salmonella*-killing, the ability of HIV-infected serum to kill without the LPS target antigen was examined using a *galE* mutant of *S.* Typhimurium D23580 lacking O-antigen polysaccharide (*15*). The mutant was fully susceptible to killing by inhibitory HIV-infected serum (Fig. 3C). Wild-type, *flgBCD*, and *ompR* mutants of D23580, deficient in the expression of flagellin and certain outer membrane proteins, respectively, served as controls and could not be killed. These results indicate that inhibitory HIV-infected sera have an inherent capacity to kill *Salmonella* and suggest that inhibitory antibodies target O-antigen, further implicating LPS IgG as the inhibitor. We investigated the effect of absorbing LPS antibodies from HIV-infected serum. Preabsorption with *S.* Typhimurium flagellin and outer membrane proteins at 100 μg/ml did not affect bactericidal activity (Fig. 3D), but preabsorption with LPS fully restored killing of *S.* Typhimurium D23580 and D19774 (Fig. 3, E and F, and fig. S9). For HIV-infected sera with partially impaired *Salmonella*-killing ability, 1 μg/ml of LPS restored normal killing (fig. S9).

Finally, LPS IgG extracted from inhibitory HIV-infected serum was added to HIV-uninfected serum. Inhibition of killing of *S.* Typhimurium D23580 and D19774 was induced at 1-10th the LPS IgG concentration present in source serum (Fig. 3, G and H), confirming LPS IgG as the inhibitor of *Salmonella*-killing. Killing of both

strains by HIV-uninfected serum was also inhibited by LPS IgG from autologous HIV-uninfected serum at 10 times the original concentration in source serum (fig. S10) (the relative concentration of LPS IgG in HIV-uninfected serum was 1-60th that in the HIV-infected serum used). This indicates that LPS IgG titer rather than the source of this antibody is critical for inhibition of *Salmonella*-killing.

Elevated IgG titers in HIV infection are characterized by antibodies to HIV viral proteins (*26*, *27*) and self-antigens (*27*, *28*). This occurs in parallel with the loss of antigen-specific antibodies; for example, to tetanus toxoid and measles (*29*). The global reduction in T-dependent (*30*, *31*) and T-independent (*18*, *31*, *32*) antibody responses after immunization in HIV-infected individuals contrasts with increased antibody to *Salmonella*-specific LPS. This indicates that immune dysregulation, not immune deficiency, accounts for impaired humoral immunity to nontyphoidal *Salmonella*. The high proportion of HIV-infected people with elevated LPS IgG suggests that high titers are not the consequence of random expansion of antigen-specific B cell clones. The explanation may relate to elevated plasma LPS titers in HIV infection secondary to microbial translocation from the gastrointestinal tract (*25*). We found no correlation between serum LPS and *S.* Typhimurium LPS antibody titers (fig. S11) and no difference between serum LPS levels in HIV-infected and -uninfected sera (P = 0.33). However, LPS is likely to be cleared from the blood by the antibody it induces in immune complexes and become localized in secondary lymphoid tissue.

We hypothesized that LPS antibodies prevent the killing of *Salmonella* by two possible mechanisms that are not mutually exclusive. One would act by diverting complement deposition away from the bacterial membrane, thereby preventing insertion of MAC into the membrane (fig. S12). The other would impede the access of antibody and/or complement to the outer membrane by cross-linking O-antigen, the distal portion of the LPS molecule. To test these hypotheses, we investigated whether the inhibitory antibodies bind O-antigen, rather than proximal lipid A and core oligosaccharide moieties (*21*). Preabsorption of inhibitory HIV-infected sera with smooth *S.* Typhimurium LPS at 100 μg/ml enabled killing of *S.* Typhimurium D23580 (Fig. 3, E and F). However, preabsorption with 100 μg/ml of lipid A or LPS from Rb, Rc, Rd, and Re rough forms of *Salmonella*, where LPS is truncated in the core oligosaccharide (*33*), did not induce killing of *Salmonella* (fig. S13, A and B). These findings indicate that inhibitory antibodies target O-antigen. We also found that inhibitory antibodies could not be removed by preabsorbing with LPS from *S.* Enteritidis (group D *Salmonella*) and *S.* Minnesota (group L *Salmonella*) (fig. S13, C and D). This provides further evidence that O-antigen is targeted by inhibitory antibodies, because LPSs from these three *Salmonella* serovars are distinguished by their non–cross-reactive O-antigens.

The concept that inhibitory antibodies act by binding O-antigen, a target distal to the *Salmonella* membrane, implies that protective bactericidal antibodies target molecules proximal to the membrane (fig. S12), an idea we have previously suggested (*15*). This conclusion is consistent with recent reports that antibodies against *S.* Typhimurium outer membrane proteins, in particular porins OMP F, C, and D, protect against *Salmonella* in the mouse (*34*). Consequently, we investigated whether such antibodies are responsible for *S.* Typhimurium–killing by serum from Africans. First, we preabsorbed serum from HIV-uninfected Malawian adults with *S.* Typhimurium outer membrane proteins, LPS, or flagellin. Although preabsorption with LPS and flagellin had no effect, killing was abrogated by preabsorption with outer membrane proteins (Fig. 4A). This indicates that antibodies

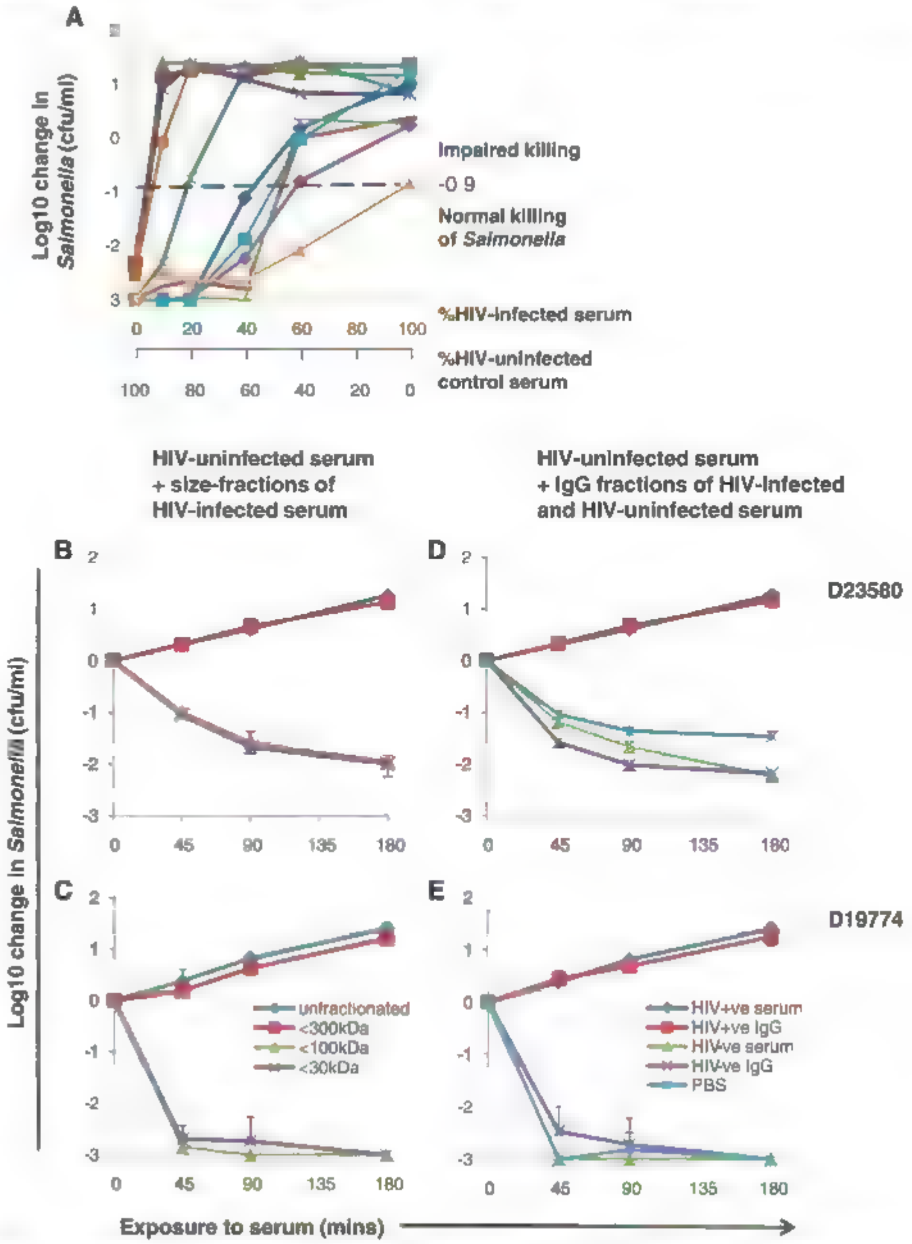

Fig. 2. Inhibition of HIV-uninfected control serum killing of NTS by HIV-infected sera with impaired *Salmonella*-killing ability. **(A)** Killing of *S.* Typhimurium A23753 at 180 min by mixed sera consisting of different percentages of HIV-infected serum (n = 12, serum from one HIV-infected person per line) and control HIV-uninfected serum. The horizontal dashed line indicates the threshold for impaired killing of *S.* Typhimurium A23753. **(B** to **E)** Inhibition of control serum killing of *S.* Typhimurium D23580 [(B) and (D)] and serum-sensitive *S.* Typhimurium D19774 [(C) and (E)] by size-fractionated [(B) and (C)] and IgG fraction [(D) and (E)] of HIV-infected serum. PBS, phosphate-buffered saline. Data are means ± SD of three experiments. Inhibition of killing of both strains of *Salmonella* by HIV-uninfected sera with a <300-kD fraction of HIV-infected serum as compared with a <100-kD fraction, and with an IgG fraction of HIV-infected serum as compared with an IgG fraction of HIV-uninfected serum was significant by Student's t test (P < 0.0001).

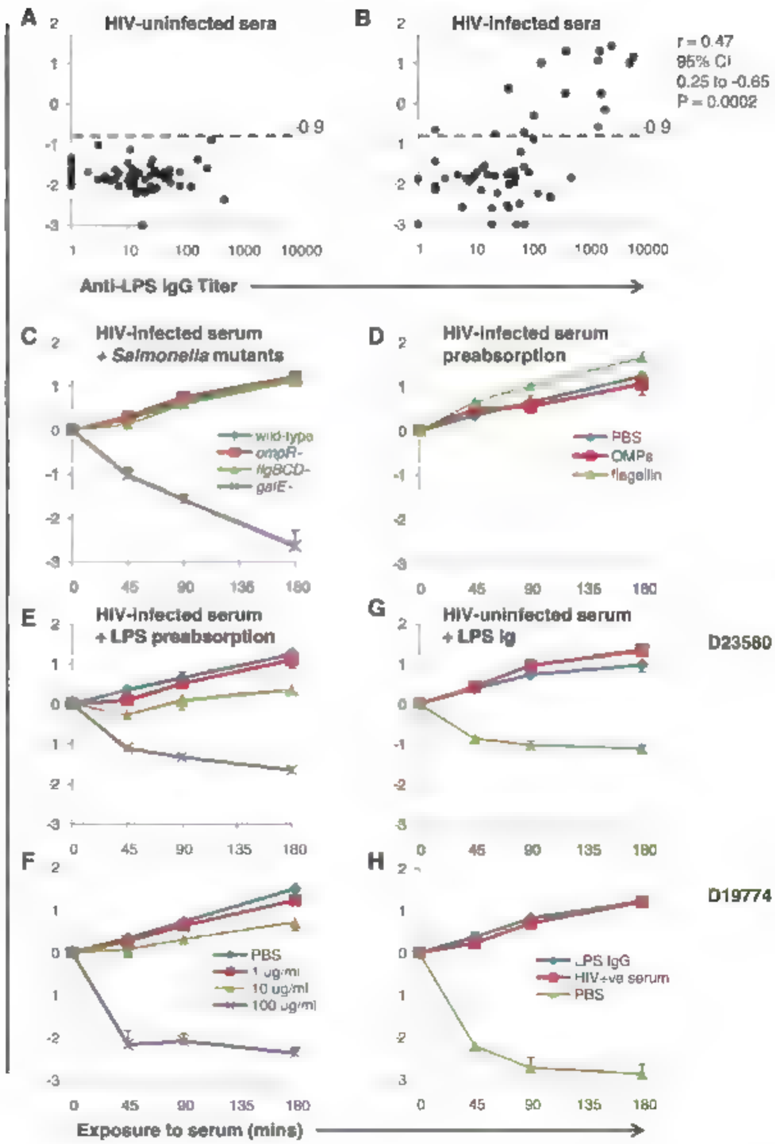

Fig. 3. LPS antibodies prevent killing of NTS by HIV-infected serum. (**A** and **B**) Killing of *S.* Typhimurium A23753 at 180 min by HIV-uninfected sera (A) and HIV-infected sera (B) compared with *S.* Typhimurium LPS IgG titer determined by enzyme-linked immunosorbent assay. The horizontal dashed line indicates the threshold for impaired killing of *S.* Typhimurium A23753. *r* is the Spearman correlation coefficient. The median IgG titer was higher in HIV-infected sera than in HIV-uninfected sera (Mann-Whitney test, $P < 0.002$; difference in medians, 20 units; 95% CI, 6.0 to 39). (**C**) Killing of indicated *S.* Typhimurium D23580 by HIV-infected serum. (**D**) Effect of preabsorbing HIV-infected serum with 100 μg/ml of *S.* Typhimurium flagellin or outer membrane proteins on killing of *S.* Typhimurium D23580. (**E** and **F**) Effect of preabsorbing HIV-infected serum with 1, 10, or 100 μg/ml LPS on serum killing of (E) D23580 and (F) D19774. (**G** and **H**) Effect of adding LPS antibodies at 1-10th the concentration in inhibitory HIV-infected source serum to HIV-uninfected serum on killing of (G) D23580 and (H) D19774. Data represent means ± SD of three experiments. Killing of both strains of *Salmonella* by HIV-infected sera preabsorbed with 100 μg/ml of LPS as compared with unabsorbed serum, and inhibition of killing of both strains of *Salmonella* by HIV-uninfected serum with exogenous LPS antibody added as compared with PBS added was significant by Student's *t* test ($P < 0.0001$).

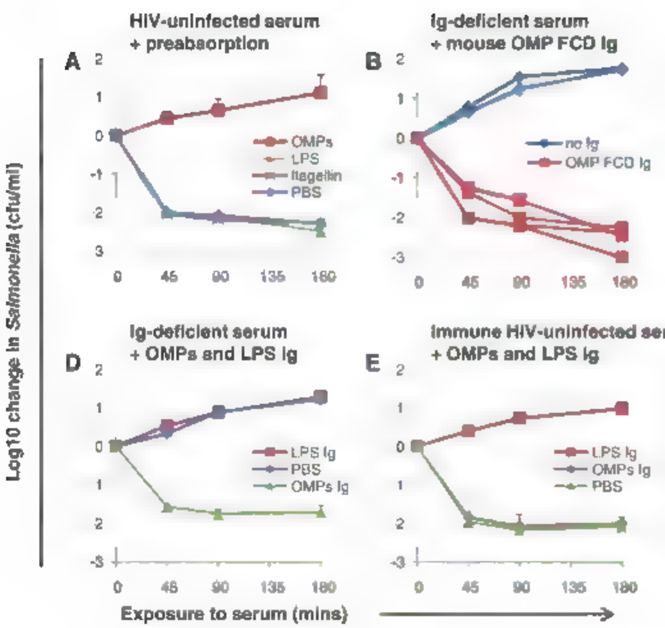

Fig. 4. Antibodies targeted against outer membrane proteins mediate African serum killing of NTS. (**A**) Effect of preabsorbing HIV-uninfected serum with 200 μg/ml of *S.* Typhimurium outer membrane proteins, flagellin, or LPS on killing of *S.* Typhimurium D23580. (**B**) Effect of adding OMP F, C, and D antibodies from four mice immunized with *S.* Typhimurium OMP F, C, and D to antibody-deficient HIV-uninfected human serum on killing of *S.* Typhimurium D23580 as compared with adding antibody from four unimmunized mice. Each line represents a $\log_{10}$ change of *Salmonella* induced by antibody from one mouse. (**C**) Effect of adding outer membrane protein antibodies from four HIV-uninfected sera (one per line) at 1-10th the concentration present in source serum, to antibody-deficient serum on killing of *S.* Typhimurium D23580. In (B) and (C), lines are superimposed. (**D** and **E**) Effect of adding outer membrane protein antibodies and LPS antibodies extracted and purified from inhibitory HIV-infected serum to antibody-deficient serum (D) or immune HIV-uninfected serum (E) on killing of *S.* Typhimurium D23580. In (A), (D), and (E), data represent means ± SD of three experiments.

against these proteins are bactericidal. Next, we immunized mice with OMP F, C, and D porins, boosted at day 14, and used heat-inactivated sera from mice at day 21 as a source of OMP F, C, and D specific antibodies. Immunized sera, but not sera from unimmunized littermates, enabled antibody-deficient human serum to kill *S.* Typhimurium D23580 (Fig. 4B). This provides further evidence that antibodies against outer membrane proteins, in particular porins, cause *Salmonella*-killing.

Finally, we purified antibodies to outer membrane proteins from HIV-uninfected and -infected Malawian sera. These antibodies, when added to antibody-deficient serum at 1-10th the concentration in source serum, enabled killing of D23580 (Fig. 4C), even when extracted from HIV-infected inhibitory serum (Fig. 4D). The outer membrane protein antibodies had no effect when added to immune HIV-uninfected serum (Fig. 4E). This contrasts with the lack of killing of *Salmonella* observed after adding LPS antibody to antibody-deficient and immune serum (Fig. 4, D and E). The findings also indicate that individual sera contain antibodies that can kill *Salmonella* and block killing of *Salmonella* (fig. S14).

These results suggest that killing of *Salmonella* by inhibitory HIV-infected sera could be restored by adding IgG from HIV-uninfected serum. We added human normal IgG immunoglobulin pooled from HIV-uninfected donors to inhibitory HIV-infected sera. This induced killing in a dose-dependent manner in three inhibitory sera but not in a fourth serum, which had an LPS antibody titer over 10 times higher than the other sera (fig. S15). Finally, killing of *Salmonella* in antibody-deficient serum could be induced or prevented by adding combinations of IgG from HIV-uninfected and inhibitory HIV-infected sera depending on the proportion of IgG from each serum (fig. S16). This supports the concept of competition between blocking antibodies and killing antibodies to *Salmonella*.

Dysregulated humoral immunity in HIV-infected Africans could contribute to their susceptibility to invasive *Salmonella* by undermining protective antibody-mediated immunity that develops within the first 2 years of life (*15*). Together with impaired cellular immunity in HIV infection, it is unsurprising that HIV-infected adults suffer from repeated episodes of *Salmonella* infection with associated high mortality (*6*, *10*). A vaccine for nontyphoidal *Salmonella* is urgently required for Africa. The current study indicates that although an O-antigen polysaccharide-based vaccine might be ineffective and increase susceptibility to life-threatening extracellular *Salmonella* growth, an outer membrane protein–based vaccine could induce protective antibodies.

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Supporting Online Material

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Materials and Methods
Figs. S1 to S16
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Teacher Quality Moderates the Genetic Effects on Early Reading

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Children's reading achievement is influenced by genetics as well as by family and school environments. The importance of teacher quality as a specific school environmental influence on reading achievement is unknown. We studied first- and second-grade students in Florida from schools representing diverse environments. Comparison of monozygotic and dizygotic twins, differentiating genetic similarities of 100% and 50%, provided an estimate of genetic variance in reading achievement. Teacher quality was measured by how much reading gain the non-twin classmates achieved. The magnitude of genetic variance associated with twins' oral reading fluency increased as the quality of their teacher increased. In circumstances where the teachers are all excellent, the variability in student reading achievement may appear to be largely due to genetics. However, poor teaching impedes the ability of children to reach their potential.

The ability to read proficiently is a critical skill, and children who fail in that skill are more likely to be retained a grade, drop out of school, and enter the juvenile criminal justice system (*1*)—all at substantial cost to society. Hence, we look to educators to ensure that children achieve proficient literacy skills, yet, a large proportion of the variability in children's reading skills is associated with nonmalleable factors like genes (*2*). Small differences in heritability (estimate of genetic influence) from twins that do versus do not share a teacher raise doubts about the effect of teachers on students' reading development (*3*). At the same time, accumulating evidence from samples of unrelated children shows that teachers do affect children's reading skill gains (*4*, *5*).

The dilemma is that research examining unrelated children cannot address whether effects are associated with genes or with the shared

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environment in families or classrooms. Genetically informative designs like twin studies use monozygotic (MZ) and dizygotic (DZ) twins to parse these effects. Comparing MZ twins, who share 100% of their genes, and DZ twins, who share ~50% of their genes, allows for inferences regarding the amount of variance associated with genes versus environment. Statistical models provide estimates of the variance associated with additive genetic (*A*), shared environmental (*C*), and nonshared environmental (*E*) factors (which serve to make people different from one another). Twin studies show that as much as 82% (*2*) of the variability in children's reading skills can be explained by genetic factors (with a median across studies ~65%), and that heritability increases once children attend school (*6*).

Twin studies also show that the influence of shared environmental factors like family and school is substantially lower than the influence of genes (*7*, *8*). However, previous twin studies may have shown small environmental effects, in part, because the environmental variance within the sample was relatively small. For example, in more homogeneous and affluent twin samples, the quality of instruction across classrooms might be relatively uniform, making the genetic influence appear larger. Advances in analytic methods for testing gene x environment interactions make it possible to assess the influence of an environmental variable on the genetic and environmental sources of variance associated with an outcome of interest, thereby allowing an examination of gene-environment interplay (*9*, *10*). For example, a few studies have examined environmental moderators such as level of parental education, which shows a positive moderation of genetic effects on word recognition (*11*) and on reading disability (*12*), wherein genetic variance was greater at higher levels of parental education. For children with high reading ability, however, parental education showed negative moderation of genetic effects (*13*), such that genetic variance was higher at lower levels of parental education. Thus, indicators of the home environment appear to have an influence on the genetic variance in extremes of reading ability. As state and national

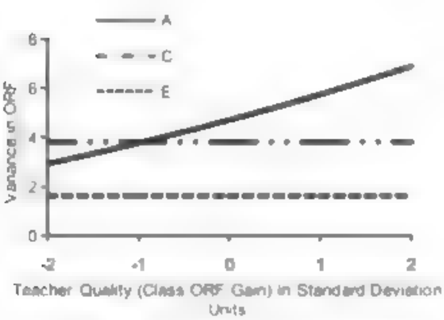

Fig. 1. Variance in twins' ORF as a function of teacher quality (class ORF gain) associated with genetic and environmental factors. A, genetic variance; C, shared environmental variance; E, nonshared environmental variance.

policy increasingly focuses on teacher quality (*14*), the effect that teachers have on the strong documented genetic foundation of reading is an important question. We address this question by examining teacher quality as an environmental moderator of genetic and environmental sources of variance in children's early reading achievement.

Data came from 280 MZ (143 female; 137 male) and 526 DZ (130 same-sex female; 128 same-sex male; 268 opposite-sex) twin pairs in the Florida Twin Project on Reading (*15*). This twin sample reflects the ethnic and socioeconomic diversity in Florida. According to parent report, 27% of the twins were African American, 33% were Hispanic, 35% were White, and the remainder was mixed or other race/ethnicity. Fifty-two percent qualified for the U.S. Free or Reduced-Priced Lunch program, where a family of four needs an annual income of less than $26,845 to qualify for free lunch or $38,203 for reduced-price lunch (*16*).

Reading achievement test data were collected on elementary school children in Florida by school staff and archived in the Progress Monitoring and Reporting Network (PMRN) (*15*, *17*). Reading skill in first and second grade was assessed using the Oral Reading Fluency test (ORF) (*15*, *18*). Twins' ORF scores near the end of first or second grade represented their reading achievement (see table S1 for descriptive statistics). Data from the twins' classmates were used to create an index of teacher quality. Specifically, growth in ORF scores for the non-twins in each teacher's class was residualized while controlling for initial ORF level (*15*). Higher scores reflected greater gains in ORF over expectations based on the average of non-twins in the class. This variable, class ORF gain, represents an environmental variable that did not rely on the twins' data or on twin or parent reports, which can introduce genetic sources of variance on environmental variables.

The intraclass correlation for ORF was 0.84 for MZ twins and 0.59 for DZ twins. Standardized estimates of genetic and environmental influence associated with variance in ORF were as follows. $A = 0.47$ (0.95 CI = 0.39 to 0.53), $C = 0.37$ (0.95 CI = 0.31 to 0.44), and $E = 0.16$ (95 CI = 0.14 to 0.19). Again, *A* represents genetic variance, *C* represents shared environmental variance, and *E* represents nonshared environmental variance. Class ORF gain and twin ORF scores were significantly correlated ($r = 0.55$, $P < 0.01$). That association was accounted for by shared environmental factors as evidenced by the highly similar magnitude of cross-twin cross-trait correlations (class ORF gain score of one twin correlated with ORF score of the co-twin) for MZ ($r = 0.46$) and DZ ($r = 0.45$) twins. Models testing moderation effects (*10*) of teacher quality on the sources of variance in ORF scores were fit to the data (*15*). Moderation can occur on the *A*, *C*, and *E* sources of variance in common to ORF and class ORF gain and on those same sources of variance that are unique to ORF (fig. S1). Moderation of unique variance in ORF provides evidence of a direct environmental effect of teacher quality on reading achievement. The best-fitting model displayed unique additive genetic variance in ORF moderated by teacher quality (see table S3 for model-fitting results). Figure 1 illustrates the positive moderation effect that was found. Genetic variance in ORF was greater at higher levels of teacher quality.

Correlations among the sources of variance contributing to ORF and class ORF gain are important to consider because they reflect other processes involved in gene-environment interplay (*9*, *15*). If, for example, there is a significant positive genetic correlation (association between the genetic factors contributing to ORF and the genetic factors contributing to class ORF gain), then this would be evidence of genetic niche-picking (*9*), wherein genetic factors contributing to the behavior (ORF) are also associated with selection of the environment (teacher quality). This was not the case as evidenced by the modest and nonsignificant genetic correlation that varied slightly from 0.16 (0.95 CI = −0.22 to 0.48) at the lowest level of teacher quality to 0.11 (0.95 CI = −0.18 to 0.27) at the highest level of teacher quality. Given that there was no moderation of the environmental sources of variance, the shared ($r = 0.96$, 0.95 CI = 0.81 to 1.0) and nonshared environment correlation ($r = 0.22$; 0.95 CI = 0.10 to 0.35) were constant across levels of teacher quality. The substantial shared environment correlation suggests environmental niche-picking processes, perhaps reflecting school-level effects such as school policies or parent preferences on placement of children in classrooms that do not vary with level of teacher quality.

Two additional methods were used to assess the effect of teacher quality on variability in ORF (*15*). Because MZ twins share all of their genes, differences between them are attributed to nonshared environmental factors. It is possible to assess such effects by using the discordant MZ twin design (*19*). Using a mean (*M*) split on ORF score, 42 discordant MZ pairs that did not share a teacher were identified. As expected, MZ twins scoring below the mean had teachers with a significantly lower class ORF gain score ($M = 58.69$; SD = 22.54) than did co-twins scoring above the mean (class ORF gain $M = 65.39$; SD = 21.74), $t(41) = -2.72$, $P = 0.005$ (1-tailed). A second analysis used all 216 MZ pairs that did not share a teacher and examined the significance of the difference in class ORF gain as a predictor of within-pair differences on ORF. Consistent with the expectation that differences in teacher quality can produce differences in early reading achievement, the class ORF gain difference within MZ pairs was a significant predictor of student ORF differences within pairs ($\beta = 3.62$; $P < 0.001$; adjusted $R^2 = 0.05$).

Instruction has an effect on achievement outcomes (*5*), but the quality of the instruction observed in classrooms is highly variable (*20*). The present results showed that teacher quality is an environmental moderator of the unique

genetic variance associated with reading achievement, demonstrating the direct influence of teacher quality on reading outcomes in children. When teacher quality is very low, genetic variance is constricted, whereas, when teacher quality is very high, genetic variance blooms. This is consistent with the bioecological model of gene x environment interaction that posits that genetic influences can be realized to their potential in more supportive environments (*21*). Reading will not develop optimally in the absence of effective instruction (*5*). If one considers that children have a range of potential reading trajectories (*22*) and effective instruction promotes stronger reading development, then in the absence of effective instruction, reading skills are less likely to develop optimally and children are less likely to achieve their potential. When children receive more effective instruction, they will tend to develop at their optimal trajectory; hence, genetic sources of influence will explain more of the individual differences in reading. When instruction is less effective, then children's learning potential is not optimized and genetic differences are left unrealized.

We assumed that the gains in reading evidenced by a classroom of students reflected teacher quality. However, classroom-level achievement gains also may be influenced by the physical classroom, classmates, resources, and the like (*20*, *23*). Moreover, there are other ways besides the value-added models used here to measure teacher quality (e.g., classroom observations, instructional artifacts) (*24*), and other ways to measure early reading achievement (e.g., decoding and reading comprehension tests). The moderation effects found for oral reading fluency might not hold for other reading measures. Furthermore, many in our sample of young twins attended schools with high poverty rates. It is possible that moderation effects of teacher quality will not be the same at older ages, when reading is more complex (*23*), or for more affluent schools, where teacher quality is typically higher and more consistent (*25*).

Twin studies can sketch the etiological architecture of reading achievement, and this particular study demonstrates the interplay between teacher quality and genetics. Emerging evidence that the effects of good instruction accumulate over a child's school career (*26*) further underscores the importance of teachers. Putting high-quality teachers in the classroom will not eliminate variability among students nor guarantee equally high achievement from all children, but ignoring teachers as a salient contributor to the classroom environment represents a missed opportunity to promote children's potential in school and their success in life.

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Supporting Online Material

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Fig. S1
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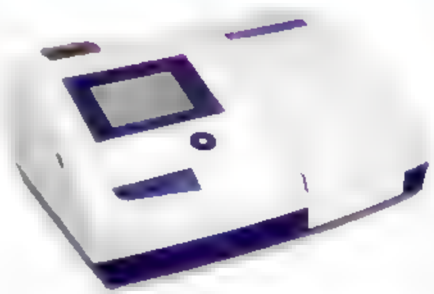

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MYTHBUSTING FOR ACADEMICS:
CONSIDERING A JOB IN BIOTECH/PHARMA

Although academia and industry differ in many ways—the speed of research, the methods of funding, and the asking of basic versus applied research questions—ultimately, the two environments are more similar than they are different. Nonetheless, several misperceptions about a career in industry tend to circulate in academia. This article attempts to clarify some of these differences and perhaps will help dispel some of the myths. By Emma Hitt


Gregory Amidon


Jeffrey Barrett

Among academics, a job in industry can represent the quintessential black box, for example, intellectual property that results from commercial science is necessarily protected. As a result though, certain myths, some of which carry extra weight because they do in fact involve a kernel of truth, tend to circulate among academics about industry. These include the idea that working in an industry job is somehow "easier" than pursuing a career in academia, or that a job in industry does not allow the opportunity to be creative or to publish work in one's own name. Also, fueled by the existence of closed off labs and lack of published results, aspersions may be cast about the quality of science practiced in industry and even the validity of the data.

MYTH: Industry Is the Easy Road

With rates of government grant funding in academia currently lower than 10 percent, no guarantees exist anymore in the academic world. "The fact is it's a lot harder being an academic scientist today than it was even 15 years ago when I made the transition," says **Harry Klee,** professor in the Plant Molecular and Cellular Biology Program at the University of Florida in Gainesville. Klee spent 11 years in industry in the plant sciences program at Monsanto before returning to academia. According to Klee, in academia, grant funding is harder to get and there are fewer jobs than there were previously. "These factors put pressure on people to work harder and harder to succeed," he says. He adds that "it's not necessarily the students with the best grades that succeed in academia—it requires a very large skill set, only one part of which is intelligence." According to Klee, these challenges in academia lead students to think they will not have to work as hard if they go into industry.

However, Klee says it's an "absolute fallacy" to think that if you cannot write well, give a good talk, or do not want to justify your spending, you should simply get a job in industry. "If you want to succeed and really get ahead, you'd better know how to write and how to talk in front of a group. At the company I worked for," he says "we had to justify what we were doing and defend it to our peers because we were competing for a pool of money."

MYTH: You Cannot Publish or Present Your Work in Industry

Another misperception is that no opportunity exists to present or publish research findings in industry. According to Klee, one of the things that fuels misperceptions about industry is the fact that the best scientists in industry generally have to keep their work confidential. "Some of the best scientists I know are in industry, and none of them will ever get the recognition they deserve because they don't present it outside the company," he says.

"Publishing may be delayed until the intellectual property considerations have been dealt with adequately."

However, it depends on the company whether research findings get published. There is an opportunity to present and publish research findings, just less than in academia, where the old adage is "publish or perish." Considerations about patenting and intellectual property exist in industry, although the same is true for academia these days, says **Alan Goldhammer,** vice president of scientific and regulatory affairs for Pharmaceutical Research and Manufacturers of America (PhRMA), an organization that represents the country's leading pharmaceutical research and biotech companies. "It just means that publishing may be delayed until the intellectual property considerations have been dealt with adequately," he says.

"The requirement to publish is not as strong in industry, obviously," says **Sarah Jones,** education and skills manager for the Association of the British Pharmaceutical Industry. "Making sure that intellectual property is secure before publication has become essential, but this is becoming more common in academia also." continued »

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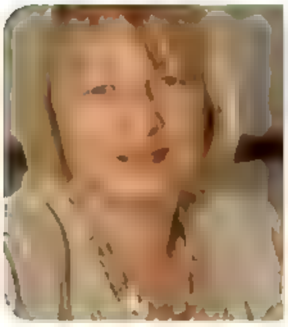

"Making sure that intellectual property is secure before publication has become essential, but this is becoming more common in academia also."
—Sarah Jones

The level of independence and also the percentage of time spent doing research may vary depending on the size of the company. According to **Jennifer Flexman,** a bioengineer who now works in technology transfer at the University of British Columbia in Vancouver, large companies such as Genentech have a strong basic research component that is not so closely related to the pipeline. "By contrast, a smaller company or startup may be more focused on the bottom line and will not provide as much opportunity for exploratory research," she says. However, at a smaller company, a scientist may wear many hats, performing nonresearch roles, such as "marketing or sales, which can be interesting, but may not be what was expected."

MYTH: There Is a Lack of Intellectual Freedom and Ability to be Creative in Industry

The misperception also exists that scientists in industry lack intellectual freedom, that they are told what to do by the company, and are not encouraged to think for themselves or pose research questions not closely related to the bottom line.

Mary Delong, director of the Office of Postdoctoral Education at Emory University in Atlanta, Georgia, says that postdocs tend to see industry as a place where they have less independence—where they cannot do "their own thing." By the time a graduate student has transitioned to being a postdoc, independence and ability to think for oneself are traits that have been well honed. "Most postdocs who avoid going into industry tend to cite lack of independence as the reason," she says.

To some extent, concerns over lack of freedom may be well founded, but the extent varies depending on the goals, structure, and especially the size of the company. "Industry jobs do tend to prize creativity, but within the confines of a predefined goal," says **Paul M. Matthews,** vice president for imaging and head of the GlaxoSmithKline Clinical Imaging Centre in Hammersmith Hospital within the company's drug discovery division. According to Matthews, there is as much freedom and as much encouragement to use creativity to find innovative solutions in industry as anywhere else.

"Certainly, in industry it is critical to work within teams to accomplish goals that are defined more by the company than by individuals," he says, "but I see industry and academia as equally exciting and valuable career options for students," says **Gregory E. Amidon,** a research professor at the University of Michigan, College of Pharmacy, in Ann Arbor and American Association of Pharmaceutical Scientists (AAPS) Fellow.

MYTH: Biased Results in Industry?

With only one approval being given for every 5,000 to 10,000 compounds entering the R&D pipeline, according to PhRMA, and the cost of bringing a drug to market estimated at over $1 billion, the pressure to produce results in industry is high. Results are directly tied to the bottom line. For this reason, science conducted in an industrial setting might be distrusted, says **Jeffrey S. Barrett,** associate professor of pediatrics at the Children's Hospital of Philadelphia, University of Pennsylvania, and member-at-large on the AAPS Executive Council.

According to Barrett, for the most part however, industry studies are "well designed, well conducted, and above reproach due to the obvious regulatory scrutiny they endure." He added that skepticism exists regarding the fact that potential safety concerns are masked by industry scientists or simply ignored. There are a few bad apples, with any occurrence of transgressions making headline news, but "the Hollywood version of this is much more interesting than the reality," he says.

Academia v. Industry—Kernels of Truth That Help Fuel Misperceptions

Although the two worlds of academia and industry are similar, distinctions do in fact exist that may help contribute to some of the misperceptions. The first is that the speed of work is usually much slower in academia as compared with industry, in which time is more directly linked to financials.

"Coming from the pharmaceutical industry, I see one of the biggest differences as being the timelines over which things in academia and industry are accomplished," says Amidon. In the pharmaceutical/biotech industry, projects move very quickly, and there is a tendency to integrate both science and problem continued »

American Association of Pharmaceutical Scientists 2009 Salary Survey

According to the American Association of Pharmaceutical Scientists 2009 Salary Survey, the median annual income of a Ph.D. with less than five years of experience working outside of academia is about $90,000.

A large majority of AAPS members employed outside of academia (68 percent) are involved with a variety of specialties, led by pharmaceutical development, biopharmaceutics/pharmacokinetics, and management/administration of research and development.

Job responsibilities held by pharmaceutical scientists outside academia include 3 percent who said they are owners or partners, 10 percent executives, 41 percent directors or managers, 19 percent supervisors or coordinators, 19 percent technical contributors, and 10 percent staff or something else. Nearly three-fourths indicated they directly or indirectly supervise others, and about a third manage a budget (over half of which are $1 million or more).

Among AAPS members working in academia, 45.2 percent of an academic's assignment time is devoted to research, with teaching requiring 32.1 percent, administration 16.1 percent, and other activities the balance of 6.6 percent.

solving into a project under a tight timeline, often less than a year, he says. By contrast, in an academic setting, timelines are generally longer and the focus is more long term, fundamental, and educational. "In academia, it is necessary to think three to five years or even more into the future with a research project," he says.

Likewise, the mechanism of financial support is different between academia and industry, and leads to differences in job function. In academia, says Amidon, there is a need to develop scientific concepts and write grants that will generate the support needed to carry out a project as well as a requirement to work closely with students and collaborators to make sure progress is being made. By contrast, in an industrial setting the focus is more directly on research, with much less focus on infrastructure issues, such as securing lab space, administrative support, and the funding of material costs. "In an industrial setting very often the goals are established by the company and senior management. It is the scientists' role to figure out the best way of accomplishing the goals that are set out," he says.

Matthews concurs that, in industry, science tends to be probably a much more "hands-on" experience, until a scientist reaches a very senior position. "Whereas in academia, a young investigator is often heavily distracted by the need to fund a laboratory, do research, and teach to demonstrate a contribution to the academic community."

Crossing the Chasm

Twenty years ago the worlds of academia and industry were more clearly delineated; now, the lines are less clear. Tentacles of academia reach into industry and vice versa. "Science in academia and science in industry are becoming a lot more similar than they used to be," says Jones with the ABPI. "Certainly, in the United Kingdom, there is an increasing push for academic research to have practical applications and for those applications to be recognized by the people doing the research." In addition, collaborations between pharmaceutical companies and academic institutions are becoming much more common, with pharmaceutical companies supporting Ph.D. studentships and providing placements for students in commercial laboratories.

Barrett agrees that a growing number of industry-based postdocs and internships are now extended to students. "As someone who trains and supports research in these disciplines, I have witnessed both the support from industry in the form of funding for postdoc training as well as the competition for students/trainees."

FEATURED PARTICIPANTS

Association of the British Pharmaceutical Industry
www.abpi.org

Emory University
www.emory.edu

GlaxoSmithKline Clinical Imaging Centre
cic.gsk.co.uk

Pharmaceutical Research and Manufacturers of America
www.phrma.org

University of British Columbia
www.ubc.ca

University of Florida, Gainesville
www.ufl.edu

University of Michigan
www.umich.edu

University of Pennsylvania
www.upenn.edu

Industry funding of universities for various studies has also increased. Academia is simultaneously expanding its relationships with industry with more "biofeeders," and commercial enterprises springing from academic endeavors, which did not occur so much 20 years ago, Delong says.

In general, starting salaries are similar between industry and academia, although in academia, early postdocs trying to prove themselves can potentially put in many more hours than an industry scientist. "Academics put in long hours competing for grants, and it's a very tough lifestyle," says Delong. "Postdocs who have gone into industry typically put in more than a 40-hour workweek, but they are not always struggling for the next grant or trying to prove themselves in the same way," she says.

Klee points out that he actually made more money when he returned to academia from industry, but the pay scales for a starting scientist and a starting assistant professor are similar. "I think it's more the attraction of industry that students feel," he says. "I've heard comments like, 'I can write a great grant proposal, and it doesn't get funded.' What that means is that there is a perception that you can be really good and not make it in academia through no fault of your own, and I think that's probably true."

Emma Hitt is a freelance medical and science writer residing in Roswell, Georgia.

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Principal Industry Facts

- The biosciences industry sector is defined as including the following four subsectors:
  - Agricultural Feedstock and Chemicals
  - Drugs and Pharmaceuticals
  - Medical Devices and Equipment
  - Research, Testing, and Medical Laboratories
- As of December 31, 2006 (the latest time point for which information is available) there were 1,452 biotechnology companies in the United States, of which 336 were publicly held.
- There were 180,000 employed in US biotech companies in 2006.
- The average annual wage of US bioscience workers was $71,000 in 2006, more than $29,000 greater than the average private-sector annual wage.

Biotechnology industry facts are available at http://bio.org/local/battelle2008/State_Bioscience_Initiatives_2008.pdf

POSITIONS OPEN

TEXAS TECH UNIVERSITY
Edward E. Whitacre Jr.
College of Engineering

The Maddox Chairs *in Energy* at Texas Tech University

The Edward E. Whitacre Jr. College of Engineering at Texas Tech University is committed to leveraging these **two exceptionally large endowed chairs at over $7 million each,** to become one of the nation's leaders in finding solutions to the world's energy challenges. The college is seeking world-class researchers in solar and sustainable energy as candidates for the Maddox Chairs.

Donovan Maddox Distinguished Engineering Chair *in Solar Energy*

Candidates are expected to have national and international reputation in solar energy based on research publications. In addition, a record of acquiring external resources to support research program building and mentoring of associates and graduate and undergraduate students is necessary. The holder of the Donovan Maddox Chair will be expected to not only bring his or her own research activities to the Whitacre College of Engineering, but also to build a collaborative community of scholars at Texas Tech dedicated to solar energy research, thereby building a world-class research program. The appointment will be as a full professor in the Whitacre College of Engineering.

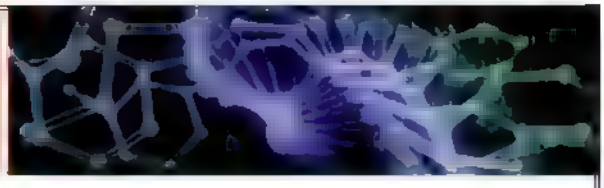
Jack Maddox Distinguished Engineering Chair *in Sustainable Energy*

Candidates with exceptional and diverse backgrounds in energy sciences and engineering are sought for this endowed position. The successful candidate will demonstrate a national and international reputation for contributions to the solution or advancement of the state of the art on a variety of research issues in the sustainable energy fields including energy efficiency, biofuels, wind power, tidal power, geothermal, and energy storage. The successful candidate along with the Donovan Maddox Chair in Solar Energy, will set the tone, vision, and the path in order to build a nationally and internationally recognized program at Texas Tech University in sustainable energy research. The appointment will be as a full professor in the Whitacre College of Engineering.

Screening will begin upon the receipt of applications and will continue until the position is filled. Candidates names will not be made public until the final stages of the search. Curriculum vitae and the names and contact information of at least four references should be submitted at www.coe.ttu.edu/maddox. To nominate a colleague for these chairs, visit www.coe.ttu.edu/maddox. Nominations can be made anonymously.

Questions about the Jack Maddox or Donovan Maddox Chairs should be directed to:
Jack Maddox and Donovan Maddox Search Committees
Texas Tech University | Whitacre College of Engineering
Box 43103 Lubbock, Texas 79409-3103 engineeringdean.coe@ttu.edu 1.800.528.5583

Texas Tech University | Whitacre College of Engineering
1.800.528.5583 | www.coe.ttu.edu/maddox



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China Novartis Institutes for Biomedical Research (CNIBR)

CNIBR is a world class fully integrated drug discovery center of excellence committed to discovering and developing innovative therapies. This newly established Novartis R&D center is dedicated to discovering innovative medicine for treating cancer, viral infection, and other diseases that are prevalent in China and Asia countries under the leadership of Dr. En Li (Head, CNIBR) and Dr. Peter Atadja (Director, Epigenetics & Drug Discovery).

We are looking for 'Drug Hunters' with demonstrated accomplishments in contributing to major milestones in drug discovery. The successful candidates will lead or work with multi-disciplinary teams and have responsibility for Ph.D. scientists and scientific associates optimizing molecules toward clinical candidates. We are seeking highly motivated and accomplished **Group Leaders, Senior investigators and Investigators** with true passion for innovative drug discovery to fill the following positions:

- Epigenetics and Transcriptional Regulation
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- Molecular and Cellular Biology
- Protein Chemistry and Structural Biology (e.g. Crystallography, NMR and Mass Spectroscopy)
- Bioinformatics and Chemoinformatics
- Postdoctoral Fellows

Qualifications and Experience:

Successful candidates should be exceptionally talented and motivated individuals, with solid education and training in biology or chemistry and proven track record of success in drug discovery. They will lead or contribute to drug discovery programs towards identification and validation of therapeutic targets, lead compounds, and discovery and refinement of drug candidates, development and characterization of both predictive and pharmacodynamic biomarkers for candidate drugs and work effectively with translational medicine experts. Additionally, the successful candidates will work under multi-site collaborative environments and with academic investigators and CROs. A Ph.D. or MD with postdoctoral experience in a relevant field plus 8+ years for Group leaders and Senior Investigators and 3+ years for Investigators work experience in biopharmaceutical industry is preferred. Postdoctoral Scientists must have completed their doctoral degree (Ph.D. or MD) within the last 2 years and have demonstrated record of research excellence.

For more details on our drug discovery programs you may contact Dr. Peter Atadja who can be reached at **peter.atadja@novartis.com**. To apply, please visit our career website **www.novartis.com/careers** and quoting Job ID 66959BR. You can find more openings by quoting "NIBR Shanghai" as the keyword.

NOVARTIS

St. Jude Children's Research Hospital

ALSAC • Danny Thomas, Founder

PROTEOMICS AND MASS SPECTROMETRY

St. Jude Children's Research Hospital (SJCRH), a premier center for biomedical investigation located in Memphis, Tennessee, USA, is expanding and developing its program in proteomics and mass spectrometry. The hospital is seeking an experienced investigator to lead this effort that will interface with the many world-class research programs within the institution. The successful candidate will have an established track record in the development and implementation of new proteomic technologies applied to a variety of biological questions. He/she will also develop a research program in mass spectrometry and proteomics that addresses fundamentally important questions relevant to the mission of the institution — to find cures for children with catastrophic diseases through research and treatment. He/she will also oversee the development of the existing mass spectrometry and proteomics core into a cutting-edge facility that will be upgraded as necessary to achieve this goal.

SJCRH is a hospital and basic research institute that focuses on the fundamental causes and treatment of catastrophic childhood diseases including cancer, infectious diseases and genetic disorders. Founded by Danny Thomas in 1962, the hospital includes some 150 basic and clinical investigators. Our interactive research environment is optimal for interdisciplinary, translational research, with opportunities to collaborate with investigators in other departments, including Biochemistry, Chemical Biology and Therapeutics, Developmental Neurobiology, Genetics and Tumor Cell Biology, Hematology, Oncology, Immunology, Infectious Diseases, Pathology, Pharmaceutical Sciences and Structural Biology. All investigators have access to state-of-the-art and well-staffed core facilities that include genomics, bioinformatics, cell imaging, protein production, molecular synthesis, X-ray crystallography, NMR spectroscopy, high-throughput chemical screening and computing. SJCRH is a National Cancer Institute Comprehensive Cancer Center and additionally receives substantial support through the fundraising efforts of the American Lebanese Syrian Associated Charities (ALSAC).

The new position is anticipated to be at the Assistant or Associate Member rank (equivalent to Assistant and Associate Professor), and a generous startup package will be provided to support laboratory and personnel needs. Candidates should have a PhD and/or MD degree and a demonstrated track record of productivity through extramural funding and high-impact publications.

Applicants should send a curriculum vitae, a 1-2-page summary of research interests and future plans and the names of three references to: **Dr. Stephen White, Proteomics and Mass Spectrometry Faculty Search Committee, Department of Structural Biology, MS 311, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678.**

St. Jude is an Equal Opportunity Employer and a Drug-Free Workplace.
Candidates receiving offers of employment will be subject to pre-employment drug testing and background checks.

www.stjude.org

Shanghai Jiao Tong University Med-X-Renji Hospital
Clinical Stem Cell Research Center
Shanghai, China

The newly established Med-X-Renji Hospital Clinical Stem Cell Research Center at Shanghai Jiao Tong University, P.R. China invites applications for researcher positions to pursue research in areas of "stem cells and tissue repair" and "cancer stem cells" at all levels. Applicants should have a Ph.D. or M.D. degree and strong expertise in stem cell research with an emphasis in one of the clinical indications such as cardiovascular, liver, neurological, bone, reproductive, and other particular disorders. Startup fund, salary and academic rank will be commensurate with qualifications of applicants.

Please submit a curriculum vitae including bibliography, statement of research interests, an outline of your proposed research, and full contact information for three references to **Professor Jiufu Luo, Associate Dean for Human Resource at Med-X Research Institute, Shanghai Jiao Tong University, Shanghai 200030, China. Telephone: 86-21-62932359; Fax: 86-21-62932302; E-mail: jfluo@sjtu.edu.cn**

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MEETINGS

MAYO CLINIC

4th MAYO CLINIC ANGIOGENESIS SYMPOSIUM: Angiogenesis and Tumor Microenvironment: Clinical Outcomes, Similarities and Discrepancies

Sponsored in part by the Department of Biochemistry and Molecular Biology and Cancer Cell Biology Program, Mayo Clinic

August 27 - 29, 2010
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Elisabetta Dejana, Ph.D.
Harold Dvorak, M.D.
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Calvin Kuo, M.D., Ph.D.
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Abstract Deadline: June 25, 2010

For more information contact **angiogenesis@mayo.edu** or call **Denise Lecy at 507-284-4070**
Early registration is advised as attendance is limited.

Register Now at: http://www.mayo.edu/cme/aug2010.html

BIOTECH/PHARMA

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Unleash your passion into a rewarding career as a Physician, Scientist or Consumer Safety Officer at the Center for Biologics Evaluation and Research! The Center for Biologics Evaluation and Research's mission is to protect and enhance the public health through the regulation of biological products including blood, vaccines, allergenics, tissues, and cellular and gene therapies. Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources (such as human, animals, and microorganisms) and are not easily identified or characterized, and many are manufactured using biotechnology. These products often represent cutting-edge biomedical research and, in time, may offer the most effective means to treat a variety of medical illnesses and conditions that presently have few or no other treatment options.

For details on qualifications and salary, please visit our Hiring Opportunities page at **http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm125465.htm**. **How to Apply:** For current vacancies and application procedures, visit **http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm103202.htm**. For future vacancies, submit CV/resume and cover letter to our resume bank to **CBER.Employment@fda.hhs.gov Attn: Job Code: Gen**

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Department of Health and Human Services
National Institutes of Health

Director, National Institutes of Health Induced Pluripotent Stem Cell Center

The NIH invites applications from outstanding candidates to establish and direct an Induced Pluripotent Stem Cell (iPSC) Center in its Intramural Research Program. This new Center will be administered by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. The successful candidate will hold a doctoral degree in a relevant field and be a recognized leader in the field of stem cell biology. S/he must have a strong track record in generating iPSCs and investigating their biology and potential therapeutic uses.

The Director will lead the newly established iPSC Center, the mission of which is to bring this exciting new technology to clinical reality within the NIH Intramural Research Program and the NIH Clinical Center. The Director will be expected to create a world-class research group that will catalyze new approaches and uses of iPSCs and differentiated cells derived from them, and/or cells trans-differentiated from somatic cells for the entire biomedical research community. The Center will collaborate with researchers to apply iPSC technologies to support their research endeavors, with a focus on the generation of clinical applications for iPSCs and/or trans-differentiated cells, and derivation of new disease-specific cell lines. The iPSC Center will promote the use of this technology and provide researchers with training to facilitate clinical development of iPSCs. The ideal candidate will be highly interactive and collaborative, and will actively engage members of the NIH intramural and the extramural research communities to identify and develop projects that have the prospect of moving to clinical trials within the NIH Clinical Center. The Director will have the opportunity to partner with the NIH Chemical Genomics Center to utilize small molecules and siRNA technologies to optimize the generation and differentiation of iPS cells. The Director will also be provided resources to direct an intramural laboratory to develop a vibrant research program in the area of stem cell biology and its clinical applications.

Salary will be commensurate with experience. A full package of benefits, including retirement, health, life, long-term care insurance, and a Thrift Savings Plan, is available.

Review of applications will begin on or about June 1, 2010, with applications being accepted until the position is filled.

Interested individuals should send a CV, a vision statement for directing the NIH iPSC Center, a statement of research interests and goals, and the names of up to five references to: Ms. Wanda White at wanda.white@nih.gov or mailed to the address below by May 31, 2010:

Bldg 31, Room 4C-12
31 Center Drive, MSC 2350
NIAMS - NIH
Bethesda, Maryland 20892-2350

DHHS and NIH are Equal Opportunity Employers.

Assistant, Associate or Full Professor(s)
Center of Excellence for Neuroscience

El Paso

The newly created Center for Excellence in Neuroscience at the Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, Texas is seeking candidates for tenure track faculty positions at Assistant, Associate or Full Professor level. This is part of a state-funded initiative to enhance research in neuroscience. The Center is seeking investigators with research interests in psychiatric genetics, autism, neurodegenerative disorders, PTSD, traumatic brain injury, neuroimaging/neuropsychiatric/neuropsychologic research in Hispanic populations or diseases of special interest to Hispanic populations.

Successful candidates are expected to develop and maintain independently funded research programs in neuroscience or a related field. The position reports to the Director of the Center of Excellence for Neuroscience.

Minimum Qualifications: M.D., D.O. or Ph.D. degree in a related field and from an accredited institution of higher education and should have funded research in an area of neuroscience (basic, clinical, or translational).

Preferred Qualifications: Candidates with demonstrated ability to perform basic scientific or clinical research and, if qualify for an Associate or Full Professor rank, must be regionally or nationally recognized in research expertise.

Center will provide start up funds and partial salary support. 50% of salary should be supported by grant funding or a combination of grant funding and clinical/teaching work. Interested candidates should submit a C.V. and letter summarizing their areas of research and career goals to: **Michael Escamilla, M.D., m.escamilla@ttuhsc.edu, Director of the Center of Excellence for Neuroscience, MSB 4009, 5001 El Paso Drive, El Paso, Texas 79905; FAX: 915-783-5205.** The position is open until filled. Application review will begin immediately.

Texas Tech University Health Sciences Center is an Equal Opportunity/Affirmative Action Employer.

Head, Electron Microscopy Facility Sloan-Kettering Institute

The Sloan-Kettering Institute (SKI) is seeking to fill a position to lead its Electron Microscopy (EM) Core Facility. SKI offers a highly interactive basic, translational and clinical cancer-focused research environment (www.ski.edu) and is located in a multi-institutional academic community. This is a non-tenure track position, fully supported by the Institution.

Description: Oversee all operations of the EM Facility including supervision of staff, operations and troubleshooting of Transmission and Scanning Electron microscopes. Provide technical consultation to the academic staff to optimize use of the microscopes to support research objectives. Provide hands-on training to facility users. Assure established standards of quality are met and that the facility remains state of the art. Perform administrative duties that include preparation of reports, budgets and charge backs to facility users.

Qualifications: Applicants must have Ph.D. in Biology or other related areas and several years of experience with conventional electron microscopy and immunoelectron microscopy in an analytical research and development or academic environment. Experience with mammalian tissue is essential. A record of productivity and management experience is desirable.

Candidates should E-mail their CV and bibliography, a cover letter describing career objectives, and the names of 3 referees in PDF format to: **cblabtrack@mskcc.org.** Inquiries regarding this position should be sent to **Diane Tabarini, PhD, Director Core Facility Operations at tabarind@mskcc.org or Alan Hall, PhD, Chairman of Cell Biology at halla@mskcc.org. Deadline: June 1, 2010.** Memorial Sloan Kettering is an affirmative action, equal opportunity employer.

Memorial Sloan-Kettering Cancer Center

www.mskcc.org

GILEAD

Principal Scientist, Biochemical Pharmacology/Molecular Pharmacology/Immunopharmacology (Respiratory)

The scope of this key role is to provide biochemical, molecular and immunopharmacology expertise for current drug discovery projects for respiratory indications. We are seeking an individual with a record of success and expertise in biochemical, molecular, and immunopharmacology related to COPD and other respiratory disorders. This individual would be responsible for contributing to the development and execution of our respiratory research strategy. This role will manage scientists within the Seattle organization, with responsibility for productivity of the in vitro pharmacology group as well as for continued development of scientific staff in the area of pulmonary pharmacology. This individual is also expected to contribute to the selection and validation of new molecular targets and to lead new project teams executing against those targets. Along with 15 years of experience with PhD in related scientific discipline, the successful individual should also have demonstrated scientific leadership through a strong publication record as well as by the development of a network of academic and industry contacts that could be utilized by Gilead. Experience in signal transduction pathways expected.

Gilead Sciences, Inc. is a research-based biopharmaceutical company that discovers, develops and commercializes innovative medicines in areas of unmet need. With each new discovery and experimental drug candidate, we seek to improve the care of patients suffering from life-threatening diseases. Our Seattle, WA site is committed to developing products for severe respiratory and infectious diseases that can help provide improved health and superior quality of life.

Qualified applicants please submit CV directly to this position at **www.gilead.com**

Gilead is an Equal Opportunity Employer.

Director
Functional Genomics Division

The United States Army Medical Research Institute of Infectious Diseases (USAMRIID) is seeking a PhD or MD level research scientist to direct a newly established, multi-year funded, Functional Genomics Division at its location on the National Interagency Biodefense Campus, Ft. Detrick, MD. This new Division is a component of a DoD Directive to map the mammalian host response to infectious viral and bacterial pathogens with the goal of developing broad spectrum therapeutics. The center will also be involved in a collaborative effort to map structural diversities in the genomes of viral and bacterial pathogens from a global repository.

The Functional Genomics Division is located in nearly 4000 ft^2 of laboratory space within USAMRIID's main research building. It is equipped with state of the art pyro-sequencing instrumentation, conventional Sanger sequencing instruments, and access to a high performance computer network. In addition, the center is part of an established research institute dedicated to the development and use of mammalian animals models (including non-human primates) for the study of highly pathogenic and infectious agents under Biosafety Level-3 and -4 containment.

The vision and goal of USAMRIID is for the Director of the Functional Genomics Division to integrate genomics research into a systems biology approach to reveal common genetic responses of both the host and the pathogen that occur during the course of infection and to use that knowledge to develop broad spectrum therapeutics.

In addition to the graduate degree requirements stated above, applicants should have a background with the following expertise:

- Scientific knowledge of systems biology, computational biology, and/or genomics research
- Published record of collaborative research in high-throughput genomic sequencing, computational biology, and bioinformatics.
- Demonstrated success in facilitating interdisciplinary research
- Management experience at a government, academic, and/or commercial research institution

Applicants should send their resume to the following internet site by **15 June 2010. USAMRIID.gc.search@amedd.army.mil**

www.nerf.be

nerf

Founded by
IMEC K.U.Leuven and VIB

NERF is the new centre for **Neuro-Electronic Research Flanders**. It is a joint basic research initiative, set up by VIB, imec and K.U.Leuven to unravel the neuronal circuitry of the human brain. NERF will investigate fundamental neuroscientific questions through collaborative, interdisciplinary research, combining nanoelectronics with neurobiology. It intends to push the boundaries of science, by zooming in on the functioning of neurons at an unprecedented level of detail. In the long run, NERF will generate new insights into the functional capabilities of the circuits of the mind as well as research methodologies and technologies for medical applications, i.e. diagnostics and treatment of disorders of the central and peripheral nervous system **(see www.NERF.be)**

NERF is housed on the imec campus in Leuven, Belgium, where researchers will work in cross-disciplinary teams, benefitting from imec's state of the art clean room infrastructure and a new 1,000m² neurolab. NERF will be composed of 5-6 teams of top-notch researchers doing world class basic research in neuro-electronics. The focus is on unraveling the electrical in- and output signals of individual neurons in a neuronal circuit in the brain of living, freely behaving animals. Devices to do so will be developed in close collaboration with imec research teams on site. By 2014, NERF aims to expand its team to about 50 international top researchers organized in 5-6 research groups, lead by a group leader. A long term backbone financial support is provided by the 3 founders and the Government of Flanders. NERF scientists will be able to work closely together with a wide range of already established research groups from the 3 founding institutions (such as neuronal communication, axon guidance, brain-computer interface, electrophysiology, ...) providing a unique leverage.

Open call for a (m/f) Director

As the director of NERF, you will be responsible for:

• developing the mission and research strategy of NERF • creating a stimulating environment and dialectic culture, which fosters talent and triggers excellence • organizing and managing the department in terms of science, tech transfer, logistics, finance and human talent

It is expected that you maintain active research interest in leading your own research program at NERF. Significant long term support will be provided to do so. You will chair the NERF management committee in which you will have final responsibility for the overall success of NERF.

The position will be a dual appointment, consisting of a tenure faculty appointment at K.U.Leuven and an additional appointment at imec as NERF director and group leader.

Requirements for the position:

NERF is searching for a dynamic, internationally recognized leader taking the challenge of building an exciting centre of excellence in neuro-electronics in Leuven, Belgium. The successful candidate

• has a Ph.D degree and is an experienced visionary scientist, widely recognized in the field • has demonstrated a strong record of scientific publications in leading scientific journals in the field. • has a track record of managing a successful research group. • has an extensive international network with a wide scope of research collaborations. • has excellent communication and negotiating skills. • has a strong will for developing a common vision and purpose for NERF

As NERF Director, you will be provided with:

• a competitive salary and benefits, including full social security and pension scheme • a long term grant for your own research group • a generous start up package for your own group • a solid funding program for NERF • full access to local and international competitive grants • dedicated lab space • privileged access to the core facilities of VIB, imec and K.U.Leuven • an exciting environment

If you are interested in this position, please send a complete publication list and CV (including at least 3 references) to jo.bury@vib.be.
Further information can be obtained from Jo Bury, chairman of the NERF board and Managing Director of VIB +32 9 244 66 11.
Closing date for applications is July 31st 2010.

Open call for (m/f) Independent Group leaders

You will investigate the functioning of the brain in a living animal. The focus is on studying the neuronal circuits by querrying the electrical activity of single or small groups of neurons in circuits using a multidisciplinary approach combining biology, genetics, imaging, electronic, micro- and nanotechnologies. Perturbation techniques to intervene into these systems in a transient, and reversible manner, such as opto-genetics, and the further miniaturization and improvement of systems opens the door for unraveling the circuitry of the brain and the way information is handled and transferred in the brain. This is of fundamental interest to NERF. Large-scale electrophysiological interactions between different populations of cells need to be monitored using advanced silicon or optical microprobe recordings. The focus is on unraveling the electrical in- and output signals of individual neurons in a neuronal circuit in the brain of living, freely behaving rodents or other small animals. In close collaboration with imec research teams you will be involved in the design and development of ground breaking devices, beyond the current state of the art. You will be empowered by working closely together with a wide range of experts from the 3 founding institutions, providing the NERF labs with a unique competitive advantage.

As a NERF group leader, you will be responsible for:

• developing an innovative research program, fitting the mission and research objectives of NERF • organizing and managing your own research group • interacting with the other NERF research groups and the research community of imec, VIB and K.U.Leuven, active in the field

Requirements for the position:

• has done several years of postdoctoral research with a proven track record of publications in leading journals in the field. • is able to set up and manage a research team of postdoctoral and postgraduate researchers and technicians. • is enthusiastic, inquisitive, focused on problem solving and a team player • is able to start research activities at NERF within a year after being selected

The package offered will consist of:

• a competitive group leader salary • a start up package • continuous funding of your own research group with 3 full time positions, in addition to your own salary • full access to local and international competitive grants • dedicated lab space • privileged access to the core facilities of VIB, imec and K.U.Leuven • an exciting environment

Candidates who are interested in this position are asked to send a complete CV and publication list and 3 letters of reference to borghs@imec.be.
Further information can be obtained from Gustaaf Borghs, NERF Co-ordinator +32 16 28 12 11. Closing date for applications is July 31st 2010.

UNIVERSITY OF MARYLAND

Assistant or Associate Professor, Molecular Nutrition

The Department of Animal and Avian Sciences at the University of Maryland invites applications for a full-time faculty position at the rank of Assistant or Associate Professor in the field of molecular nutrition. We seek an outstanding candidate that employs state-of-the-art molecular and genetic approaches to study mechanisms of nutrient cofactor uptake, transport, metabolism, and growth at the cellular and organismal level in animal models with relevance to agriculture. The candidate will strengthen and bridge the department's research areas of Nutrient Utilization, Genetics and Cell Biology, and Reproduction and Development. A strong record of independent research documented through publications and discoveries is essential. A record of Federal funding is preferable. A strong interest in graduate education is important. Teaching responsibilities include Vitamins and Minerals as well as Molecular Nutrition courses. Applicants must have a Doctor of Philosophy or equivalent degree. Salary and rank will be commensurate with experience. Additional information can be obtained at **http://ansc.umd.edu/**. The University of Maryland at College Park is the flagship campus of the University of Maryland System located in the heart of the Baltimore-Washington research corridor, just 15 minutes from downtown Washington, D.C.

Interested candidates should apply for this position electronically through **https://jobs.umd.edu, Position Number 103161**. Please submit a curriculum vitae, a description of research accomplishments and proposed research program, a summary of teaching interests, and three letters of reference addressed to **Dr. Iqbal Hamza, Chair, Molecular Nutritionist Search Committee, Department of Animal and Avian Sciences, University of Maryland, College Park, Maryland 20742.** Application deadline is **June 15, 2010** or until a suitable applicant is identified.

University of Maryland is an Equal Opportunity Employer and is committed to building a broadly diverse and inclusive faculty and staff.

The Gruss Lipper Family Foundation invites you to apply to the Gruss Lipper Post-Doctoral Fellowship Program

Eligibility:

- Israeli citizenship
- Candidates must have completed PhD and/or MD/PhD degrees in the Biomedical Sciences at an accredited Israeli University/Medical School or be in their final year of study
- Candidates must have been awarded a postdoctoral position in U.S. host research institution

Details regarding the fellowship and the application process are available at:
ea@gruss.com

POSITIONS OPEN

UAHuntsville
THE UNIVERSITY OF ALABAMA IN HUNTSVILLE

VISITING FACULTY POSITIONS
University of Alabama in Huntsville
Department of Biological Sciences

The Department of Biological Sciences at the University of Alabama in Huntsville invites applications for three visiting **ASSISTANT PROFESSOR** positions. A Ph.D. degree in biology or a related discipline is required. Teaching responsibilities for the three positions will be in the areas of cell biology, microbiology, and animal physiology. These are one-year positions with the possibility of a second year. The Department of Biological Sciences is housed in the Shelby Center for Science and Technology with spacious, well-equipped teaching halls and laboratory facilities. Huntsville, a mid-sized city in northern Alabama, is the home of NASA Marshall Space Flight Center, the Redstone Arsenal, and one of the nation's largest research parks. The area boasts a reasonable cost of living and ample recreational and cultural opportunities. Please visit the departmental **website: http://www.uah.edu/biology** to learn more about the Department. The starting date for the positions will be August 2010. To apply, please send curriculum vitae along with a statement of teaching interests and the names and contact information for three professional references to:

Dr. Lynn Boyd
Search Committee Chair
Department of Biological Sciences
University of Alabama in Huntsville
Huntsville, AL 35899

Review of applications will begin May 1, 2010, and will continue until the positions are filled. *Women and minorities are encouraged to apply. The University of Alabama in Huntsville is an Affirmative Action, Equal Opportunity Institution.*

UPPSALA UNIVERSITET

POSTDOCTORAL FELLOW
in Single Molecule Imaging
at Uppsala University, Sweden

The Postdoctoral fellow will work with the construction of optical microscopes for single-molecule tracking and superresolution imaging in living cells. Suitable background is a Ph.D. in experimental biophysics and experience in advanced fluorescence microscopy.

More information and application procedures available at **website: http://www.uu.se/job**.

POSITIONS OPEN

VCU Medical Center
Virginia Commonwealth University

POSTDOCTORAL RESEARCH POSITION
Role of the Pleiotropic Mediator, Sphingosine-1-Phosphate, in Health and Diseases

A Postdoctoral position is open for a talented scientist to be part of exciting projects directed by **Dr. Sarah Spiegel**, Chair of Biochemistry and Molecular Biology, studying functions of sphingosine-1-phosphate in novel signaling pathways important for inflammation and cancer (see *Science* **325**:1254, 2009). Candidates must have a Ph.D. and should have experience in biochemistry, molecular and cellular biology, or immunology. Submit a cover letter with curriculum vitae and three reference letters to: **Dr. Sarah Spiegel, Virginia Commonwealth University, School of Medicine, Richmond, VA 23298, Attn: Dr. Michael Maceyka, e-mail: mwmaceyka@vcu.edu.**

CANCER GENOMICS
UNIVERSITY OF SOUTH CAROLINA

The Department of Biological Sciences at the University of South Carolina invites applications for a tenure-track position at the rank of **ASSISTANT** or **ASSOCIATE PROFESSOR** in the broad area of cancer genomics. Candidates are sought with a strong background in genomic and epigenomic approaches to identify and characterize cancer-related genes and pathways. Preference given individuals applying results of cell line and animal model studies to human cancer.

Applicants should have Ph.D. or M.D. in an appropriate discipline along with postdoctoral experience. Selection will be based on excellence in research, and applicants will be expected to develop productive research programs, establish/maintain extramural funding, and contribute to undergraduate and graduate teaching in the Department of Biological Sciences. Additional responsibilities include scientific oversight of the Human Tissue Biorepository maintained at the University. The individual will have opportunities to interact with researchers in the Department of Biological Sciences (**website: http://www.biol.sc.edu/**) as well as with a growing research group within USC's Center for Colon Cancer Research (**website: http://cccr.sc.edu/**), which provides a highly multidisciplinary environment, with access to state-of-the-art animal, imaging, and genomics core facilities (**website: http://engencore.sc.edu/**). Interactions are maintained with research scientists from several departments including those in the Arnold School of Public Health (**website: http://www.sph.sc.edu**), the South Carolina School of Pharmacy (**website: http://www.sccp.sc.edu/**), and the Cancer Prevention and Control Program (**website: http://cpcp.sph.sc.edu/**).

Applicants should send curriculum vitae, description of research accomplishments, future research objectives, and three letters of reference to: **Dr. Rekha Patel, Department of Biological Sciences, University of South Carolina, Columbia, SC 29208. E-mail: patelr@biol.sc.edu.** Electronic submission is preferred. Review of applications will begin May 15, 2010, and will continue until the position has been filled.

The University of South Carolina is an Affirmative Action, Equal Opportunity Employer. Women and minorities are encouraged to apply. The University of South Carolina does not discriminate in educational or employment opportunities or decisions for qualified persons on the basis of race, color, religion, sex, national origin, age, disability, sexual orientation, or veteran status.

MARKETPLACE

PNAS Congratulates
2009 Cozzarelli Prize Recipients

The *Proceedings of the National Academy of Sciences* (PNAS) has selected six outstanding articles for the 2009 Cozzarelli Prize, in recognition of their scientific excellence and originality. Winners were selected from the 3,800 research articles published in PNAS in 2009 and represent exceptional contributions to the six broadly defined classes under which the National Academy of Sciences is organized.

2009 COZZARELLI PRIZE RECIPIENTS

Class I: Physical And Mathematical Sciences
Physical and biogeochemical modulation of ocean acidification in the central North Pacific
John E. Dore, Roger Lukas, Daniel W. Sadler, Matthew J. Church, and David M. Karl
(2009) PNAS 106:12235–12240

Class II: Biological Sciences
Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout
Owen M. Woodward, Anna Köttgen, Josef Coresh, Eric Boerwinkle, William B. Guggino, and Michael Köttgen
(2009) PNAS 106:10338–10342

Class III: Engineering and Applied Sciences
Nanoscale magnetic resonance imaging
C. L. Degen, M. Poggio, H. J. Mamin, C. T. Rettner, and D. Rugar
(2009) PNAS 106:1313–1317

Class IV: Biomedical Sciences
Hypersensitivity to contact inhibition provides a clue to cancer resistance of naked mole-rat
Andrei Seluanov, Christopher Hine, Jorge Azpurua, Marina Feigenson, Michael Bozzella, Zhiyong Mao, Kenneth C. Catania, and Vera Gorbunova
(2009) PNAS 106:19352–19357

Class V: Behavioral and Social Sciences
Neural correlates of admiration and compassion
Mary Helen Immordino-Yang, Andrea McColl, Hanna Damasio, and Antonio Damasio
(2009) PNAS 106:8021–98026

Class VI: Applied Biological, Agricultural, and Environmental Sciences
Wild birds of declining European species are dying from a thiamine deficiency syndrome
Lennart Balk, Per-Åke Hägerroth, Gun Åkerman, Marsha Hanson, Ulla Tjärnlund, Tomas Hansson, Gunnar Thor Hallgrimsson, Yngve Zebühr, Dag Broman, Torsten Mörner, and Henrik Sundberg
(2009) PNAS 106:12001–12006






Podcast interviews with the authors will be available at www.pnas.org/site/misc/podcasts.shtml

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